

Appendix A. Selected internet links

Appendix Table A1. Internet links for radiotherapy organizations

<i>Organization</i>	<i>URL address</i>
Deutsche Gesellschaft für Radioonkologie	http://www.degro.org/jsp_public/cms/index.jsp
European Society for Therapeutic Radiology and Oncology	http://www.estroweb.org/estro/index.cfm
American Society for Therapeutic Radiology and Oncology	http://www.astro.org/
National Association for Proton Therapy	http://www.proton-therapy.org/
Particle Therapy Cooperative Group	http://ptcog.web.psi.ch/

(Last accessed 06/16/2008)

Appendix Table A2. Internet links for particle beam instrumentation companies

<i>Company</i>	<i>URL address</i>
Ion Beam Applications (IBA) Solutions	http://www.iba-worldwide.com/
Still River Systems Inc	http://www.stillriversystems.com/
Optivus Proton Therapy	http://www.optivus.com/
Siemens	http://www.medical.siemens.com/
Hitachi: Proton beam Therapy	http://www.pi.hitachi.co.jp/rd-eng/product/industrial-sys/accelerator-sys/proton-therapy-sys/proton-beam-therapy/index.html
ACCEL Instruments	http://www.proton-therapy.com/

(Last accessed 06/16/2008)

Appendix Table A3. Internet links for particle beam treatment centers in the USA

<i>Center/Institute</i>	<i>URL address</i>
Francis H. Burr Proton Therapy Center (NPTC)	http://www.massgeneral.org/cancer/about/providers/radiation/proton/index.asp
Loma Linda University Proton Therapy Center	http://www.llu.edu/proton/index.html
University of California, Crocker Nuclear Lab	http://media.cnl.ucdavis.edu/crocker/website/default.php
Midwest Proton Radiotherapy Institute, Bloomington	http://www.mpri.org/
M.D. Anderson Proton Therapy Center, Houston	http://www.mdanderson.org/care_centers/radiationonco/ptc/
University of Florida Proton Therapy Institute, Jacksonville	http://www.floridaproton.org/

(Last accessed 06/16/2008)

Appendix B. Ovid Medline search strategy

<i>ID</i>	<i>Search term</i>	<i>Citations</i>
1	particle beam.mp.	157
2	heavy ion*.mp. or exp Heavy Ions/	1411
3	light ion*.mp.	115
4	charged particle*.mp.	1114
5	boron neutron captrure.mp.	0
6	hadron\$.mp.	168
7	proton\$.mp. or exp Protons/	70128
8	Carbon ion.mp.	225
9	C-ion\$.mp.	152
10	helium ion\$.mp.	202
11	He-ion\$.mp.	26
12	exp Alpha Particles/ or alpha irradiation.mp.	1872
13	(LET or linear energy transfer).mp.	12772
14	exp Particle Accelerators/	5736
15	or/1-14	90173
16	exp Radiotherapy/	98150
17	exp Radiotherapy, High-Energy/	14620
18	irradiation.mp. or exp Pituitary Irradiation/ or exp Lymphatic Irradiation/ or exp Cranial Irradiation/	107651
19	beam therap*.mp.	1047
20	pion* therap*.mp.	29
21	piontherap*.mp.	0
22	proton* therap*.mp.	380
23	protontherap*.mp.	55
24	neutron capture therap*.mp.	1288
25	neutron therap*.mp.	551
26	neutrontherap*.mp.	12
27	ion\$ therap*.mp.	152
28	iontherap*.mp.	2
29	beam irradiation.mp.	1806
30	beam radiation.mp.	2485
31	radiation therap*.mp.	34480
32	particle therap*.mp.	111
33	hadron\$therap*.mp.	39
34	hadrontherap*.mp.	39
35	particle beam therap*.mp.	10
36	charged particle therap*.mp.	47
37	or/16-36	195909
38	15 and 37	7458
39	limit 38 to humans	4776
40	remove duplicates from 39	4747

Appendix C. Table of eligible studies

<i>Citation</i>	<i>PMID</i>
<i>Bladder</i>	
Miyanaga N, Ami Y, Ohtani M et al. Clinical study of proton radiotherapy in urological cancers. [Japanese]. Nippon Hinyokika Gakkai Zasshi - Japanese Journal of Urology 81(2):251-7, 1990.	2157915
Hata M, Miyanaga N, Tokuuye K et al. Proton beam therapy for invasive bladder cancer: a prospective study of bladder-preserving therapy with combined radiotherapy and intra-arterial chemotherapy. International Journal of Radiation Oncology, Biology, Physics 64(5):1371 -9, 2006.	16580495
Tsuji H, Akaza H, Ohtani M et al. Preliminary results of bladder-preserving therapy with definitive radiotherapy and intraarterial infusion of chemotherapy. Strahlentherapie und Onkologie 170 (9):531 -7, 1994.	7940124
<i>Bone</i>	
Delaney TF, Park L, Goldberg SI et al. Radiotherapy for local control of osteosarcoma. International Journal of Radiation Oncology, Biology, Physics 61(2):492-8, 2005.	15667972
Kamada T, Tsuji H, Tsuji H et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. Journal of Clinical Oncology 19(20), 4466-4471.	12431970
Reimers M, Castro JR, Linstadt D et al. Heavy charged particle therapy of bone and soft tissue sarcoma. A phase I-II trial of the University of California Lawrence Berkeley Laboratory and the Northern California Oncology Group. American Journal of Clinical Oncology 9(6):488-93, 1986.	2431614
Timmermann B, Schuck A, Niggli F et al. Spot-scanning proton therapy for malignant soft tissue tumors in childhood: First experiences at the Paul Scherrer Institute. International Journal of Radiation Oncology, Biology, Physics 67(2):497-504, 2007.	17084557
Weber DC, Rutz HP, Bolsi A et al. Spot scanning proton therapy in the curative treatment of adult patients with sarcoma: the Paul Scherrer institute experience. International Journal of Radiation Oncology, Biology, Physics 69(3):865-71, 2007.	17606333
Zhang H, Yoshikawa K, Tamura K et al. [(11)C]methionine positron emission tomography and survival in patients with bone and soft tissue sarcomas treated by carbon ion radiotherapy. Clinical Cancer Research 10(5):1764-72, 2004.	15014030
<i>Breast</i>	
Bush DA, Slater JD, Garberoglio C, Yuh G, Hocko JM, Slater JM. A technique of partial breast irradiation utilizing proton beam radiotherapy: comparison with conformal x-ray therapy.[see comment]. Cancer Journal 13(2):114 -8, 2007.	17476139
Kozak KR, Smith BL, Adams J et al. Accelerated partial-breast irradiation using proton beams: initial clinical experience. International Journal of Radiation Oncology, Biology, Physics 66(3):691-8, 2006.	17011445
<i>Gastrointestinal</i>	
Castro JR, Saunders WM, Quivey JM et al. Clinical problems in radiotherapy of carcinoma of the pancreas. American Journal of Clinical Oncology 5(6):579-87, 1982.	6762086
Castro JR, Chen GT, Pitluck S et al. Helium charged-particle radiotherapy of locally advanced carcinoma of the esophagus, stomach, and biliary tract. American Journal of Clinical Oncology 6 (6):629 -37, 1983.	6637875
Koyama S, Tsuji H, Yokota H et al. Proton beam therapy for patients with esophageal carcinoma. Japanese Journal of Clinical Oncology 24 (3):144 -53, 1994	8007424

<i>Citation</i>	<i>PMID</i>
Linstadt D, Quivey JM, Castro JR et al. Comparison of helium-ion radiation therapy and split-course megavoltage irradiation for unresectable adenocarcinoma of the pancreas. Final report of a Northern California Oncology Group randomized prospective clinical trial. <i>Radiology</i> 168 (1):261-4, 1988.	3132732
Schoenthaler R, Phillips TL, Castro J, Efird JT, Better A, Way LW. Carcinoma of the extrahepatic bile ducts. The University of California at San Francisco experience. <i>Annals of Surgery</i> 219 (3):267 -74, 1994.	8147607
Schoenthaler R, Castro JR, Halberg FE, Phillips TL. Definitive postoperative irradiation of bile duct carcinoma with charged particles and/or photons. <i>International Journal of Radiation Oncology, Biology, Physics</i> 27 (1):75 -82, 1993.	8365945
Sugahara S, Tujii H, Tuji H, Tatzuzaki H, Ohara K, Itai Y. [The value of frequent positioning of treatment field in radiotherapy of esophageal cancer]. [Japanese]. <i>Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica</i> 52 (9):1308 -14, 1992	1437536
Sugahara S, Tokuyue K, Okumura T et al. Clinical results of proton beam therapy for cancer of the esophagus. <i>International Journal of Radiation Oncology, Biology, Physics</i> 61 (1):76 -84 , 2005	15629597
<i>Head and Neck</i>	
Al-Mefty O, Borba LA. Skull base chordomas: a management challenge. <i>Journal of Neurosurgery</i> 86 (2):182 -9 , 1997	9010416
Austin-Seymour M, Munzenrider J, Goitein M et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. <i>Journal of Neurosurgery</i> 70 (1):13-7 , 1989	2535872
Austin-Seymour M, Munzenrider J, Linggood R et al. Fractionated proton radiation therapy of cranial and intracranial tumors. <i>American Journal of Clinical Oncology</i> 13(4):327 -30 , 1990	2165739
Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. <i>International Journal of Radiation Oncology, Biology, Physics</i> 31 (3):577 -81 , 1995	7852123
Berson AM, Castro JR, Petti P et al. Charged particle irradiation of chordoma and chondrosarcoma of the base of skull and cervical spine: the Lawrence Berkeley Laboratory experience. <i>International Journal of Radiation Oncology, Biology, Physics</i> 15 (3):559 -65, 1988.	3138208
Castro JR, Linstadt DE, Bahary JP et al. Experience in charged particle irradiation of tumors of the skull base: 1977-1992.[see comment]. [Review] [35 refs]. <i>International Journal of Radiation Oncology, Biology, Physics</i> 29 (4):647 -55 , 1994.	8040010
Castro JR, Reimers MM. Charged particle radiotherapy of selected tumors in the head and neck. <i>International Journal of Radiation Oncology, Biology, Physics</i> 14(4):711-20, 1988.	3350726
Castro JR, Phillips TL, Prados M et al. Neon heavy charged particle radiotherapy of glioblastoma of the brain. <i>International Journal of Radiation Oncology, Biology, Physics</i> 38 (2):257 -61 , 1997	9226311
Colli B, Al-Mefty O. Chordomas of the craniocervical junction: follow-up review and prognostic factors. <i>Journal of Neurosurgery</i> 95 (6):933 -43 , 2001	11765837
Debus J, Haberer T, Schulz-Ertner D et al. [Carbon ion irradiation of skull base tumors at GSI. First clinical results and future perspectives]. [German]. <i>Strahlentherapie und Onkologie</i> 176 (5):211 -6, 2000	10847117
Fagundes MA, Hug EB, Liebsch NJ, Daly W, Efird J, Munzenrider JE. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. <i>International Journal of Radiation Oncology, Biology, Physics</i> 33 (3):579 -84 , 1995	7558946

<i>Citation</i>	<i>PMID</i>
Fitzek MM, Thornton AF, Harsh G et al. Dose-escalation with proton/photon irradiation for Dumas-Duport lower-grade glioma: results of an institutional phase I/II trial. <i>International Journal of Radiation Oncology, Biology, Physics</i> 51(1):131-7, 2001.	11516862
Fitzek MM, Thornton AF, Varvares M et al. Neuroendocrine tumors of the sinonasal tract. Results of a prospective study incorporating chemotherapy, surgery, and combined proton-photon radiotherapy. <i>Cancer</i> 94 (10):2623 -34 , 2002	12173330
Fuss M, Hug EB, Schaefer RA et al. Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. <i>International Journal of Radiation Oncology, Biology, Physics</i> 45 (5):1117 -26 , 1999	10613303
Gridley DS, Loredon LN, Slater JD et al. Pilot evaluation of cytokine levels in patients undergoing radiotherapy for brain tumor. <i>Cancer Detection & Prevention</i> 22 (1):20 -9, 1998	9466045
Hasegawa A, Mizoe JE, Mizota A, Tsujii H. Outcomes of visual acuity in carbon ion radiotherapy: analysis of dose-volume histograms and prognostic factors. <i>International Journal of Radiation Oncology, Biology, Physics</i> 64 (2):396 -401, 2006	16182466
Hug EB, DeVries A, Thornton AF et al. Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy. <i>Journal of Neuro-Oncology</i> 48 (2):151 -60, 2000	11083080
Hug EB, Loredon LN, Slater JD et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base.[see comment]. <i>Journal of Neurosurgery</i> 91 (3):432 -9, 1999.	10470818
Hug EB, Muentner MW, Archambeau JO et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. <i>Strahlentherapie und Onkologie</i> 178(1):10-7, 2002	11977386
Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of pediatric base of skull tumors. <i>International Journal of Radiation Oncology, Biology, Physics</i> 52(4):1017 -24 , 2002	11958897
Igaki H, Tokuyama K, Okumura T et al. Clinical results of proton beam therapy for skull base chordoma. [Review] [38 refs]. <i>International Journal of Radiation Oncology, Biology, Physics</i> 60(4):1120 -6, 2004	15519783
Kishimoto R, Mizoe JE, Komatsu S, Kandatsu S, Obata T, Tsujii H. MR imaging of brain injury induced by carbon ion radiotherapy for head and neck tumors. <i>Magnetic Resonance in Medical Sciences</i> 4(4):159 -64 , 2005	16543700
McAllister B, Archambeau JO, Nguyen MC et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease-related morbidities. <i>International Journal of Radiation Oncology, Biology, Physics</i> 39 (2):455 -60 , 1997	9308950
Mizoe JE, Tsujii H, Hasegawa A et al. Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. <i>International Journal of Radiation Oncology, Biology, Physics</i> 69 (2):390-6, 2007.	17459607
Mizoe JE, Tsujii H, Kamada T et al. Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer.[see comment]. <i>International Journal of Radiation Oncology, Biology, Physics</i> 60(2):358-64, 2004.	15380567
Nishimura H, Ogino T, Kawashima M et al. Proton-beam therapy for olfactory neuroblastoma. <i>International Journal of Radiation Oncology, Biology, Physics</i> 68(3):758 -62 , 2007	17398027
Noel G, Feuvret L, Calugaru V et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. <i>Acta Oncologica</i> 44 (7):700 -8 , 2005	16227160

<i>Citation</i>	<i>PMID</i>
Noel G, Feuvret L, Dhermain F et al. [Chordomas of the base of the skull and upper cervical spine. 100 patients irradiated by a 3D conformal technique combining photon and proton beams]. [French]. <i>Cancer Radiotherapie</i> 9(3):161 -74 , 2005	15979920
Noel G, Feuvret L, Ferrand R, Boisserie G, Mazon JJ, Habrand JL. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. <i>Neurosurgery</i> 55 (6):1252 -60; discussion 1260 -2, 2004	15574207
Noel G, Habrand JL, Helfre S et al. Proton beam therapy in the management of central nervous system tumors in childhood: the preliminary experience of the Centre de Protontherapie d'Orsay. <i>Medical & Pediatric Oncology</i> 40 (5):309 -15, 2003	12652619
Noel G, Habrand JL, Jauffret E et al. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. <i>Strahlentherapie und Onkologie</i> 179 (4):241 -8 , 2003	12707713
Noel G, Habrand JL, Mammar H et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protontherapie D'Orsay experience. <i>International Journal of Radiation Oncology, Biology, Physics</i> 51 (2):392 -8 , 2001	11567813
Noel G, Jauffret E, Crevoisier RD et al. [Radiation therapy for chordomas and chondrosarcomas of the base of the skull and cervical spine]. [French]. <i>Bulletin du Cancer</i> 89 (7 -8):713 -23, 2002	12206985
O'Connell JX, Renard LG, Liebsch NJ, Efirid JT, Munzenrider JE, Rosenberg AE. Base of skull chordoma. A correlative study of histologic and clinical features of 62 cases. <i>Cancer</i> 74 (8):2261 -7 , 1994	7922977
Pommier P, Liebsch NJ, Deschler DG et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. <i>Archives of Otolaryngology -- Head & Neck Surgery</i> 132 (11):1242 -9, 2006	17116822
Rosenberg AE, Nielsen GP, Keel SB et al. Chondrosarcoma of the base of the skull: a clinicopathologic study of 200 cases with emphasis on its distinction from chordoma. <i>American Journal of Surgical Pathology</i> 23(11):1370 -8 , 1999	10555005
Santoni R, Liebsch N, Finkelstein DM et al. 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. <i>International Journal of Radiation Oncology, Biology, Physics</i> 41 (1):59 -68, 1998	9588918
Saunders WM, Chen GT, ustin-Seymour M et al. Precision, high dose radiotherapy. II. Helium ion treatment of tumors adjacent to critical central nervous system structures. <i>International Journal of Radiation Oncology, Biology, Physics</i> 11(7):1339-47, 1985.	4008290
Schulz-Ertner D, Haberer T, Jakel O et al. Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions. <i>International Journal of Radiation Oncology, Biology, Physics</i> 53(1):36-42, 2002.	12007939
Schulz-Ertner D, Haberer T, Scholz M et al. Acute radiation-induced toxicity of heavy ion radiotherapy delivered with intensity modulated pencil beam scanning in patients with base of skull tumors. <i>Radiotherapy & Oncology</i> 64 (2):189 -95, 2002	12242129
Schulz-Ertner D, Karger CP, Feuerhake A et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. <i>International Journal of Radiation Oncology, Biology, Physics</i> 68(2):449 -57 , 2007	17363188
Schulz-Ertner D, Nikoghosyan A, Didinger B et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. <i>Cancer</i> 104 (2):338 -44 , 2005	15937907
Schulz-Ertner D, Nikoghosyan A, Didinger B, Debus J. Carbon ion radiation therapy for chordomas and low grade chondrosarcomas--current status of the clinical trials at GSI. <i>Radiotherapy & Oncology</i> 73 Suppl 2:S53 -6, 2004	15971310

<i>Citation</i>	<i>PMID</i>
Schulz-Ertner D, Nikoghosyan A, Jakel O et al. Feasibility and toxicity of combined photon and carbon ion radiotherapy for locally advanced adenoid cystic carcinomas. <i>International Journal of Radiation Oncology, Biology, Physics</i> 56 (2):391 -8, 2003	12738314
Schulz-Ertner D, Nikoghosyan A, Thilmann C et al. Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base. Results in 67 patients. <i>Strahlentherapie und Onkologie</i> 179 (9):598-605, 2003.	14628125
Schulz-Ertner D, Nikoghosyan A, Thilmann C et al. Results of carbon ion radiotherapy in 152 patients. <i>International Journal of Radiation Oncology, Biology, Physics</i> 58 (2):631 -40 , 2004	14751537
Slater JD, ustin-Seymour M, Munzenrider J et al. Endocrine function following high dose proton therapy for tumors of the upper clivus. <i>International Journal of Radiation Oncology, Biology, Physics</i> 15 (3):607 -11, 1988	3138212
Slater JD, Yonemoto LT, Mantik DW et al. Proton radiation for treatment of cancer of the oropharynx: early experience at Loma Linda University Medical Center using a concomitant boost technique. <i>International Journal of Radiation Oncology, Biology, Physics</i> 62 (2):494-500, 2005.	15890592
Suit HD, Goitein M, Munzenrider J et al. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. <i>Journal of Neurosurgery</i> 56 (3):377 -85 , 1982	7057235
Terahara A, Niemierko A, Goitein M et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. <i>International Journal of Radiation Oncology, Biology, Physics</i> 45 (2):351-8, 1999	10487555
Tokuuye K, Akine Y, Kagei K et al. Proton therapy for head and neck malignancies at Tsukuba. <i>Strahlentherapie und Onkologie</i> 180 (2):96 -101 , 2004	14762662
Weber DC, Chan AW, Lessell S et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. <i>Radiotherapy & Oncology</i> 81 (3):243 -9, 2006	17050017
Weber DC, Rutz HP, Pedroni ES et al. Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. <i>International Journal of Radiation Oncology, Biology, Physics</i> 63(2):401 -9, 2005	16168833
Yoshii Y, Maki Y, Narushima A et al. [Use of radiotherapy by high-energy protons in the postoperative treatment of brain tumors]. [Japanese]. <i>Neurologia Medico-Chirurgica</i> 26 (3):219 -26 , 1986	2426616
Yoshii Y, Takano S, Tsurushima H et al. Normal brain damage after radiotherapy of brain tumours. <i>Clinical Oncology (Royal College of Radiologists)</i> 3(5):278 -82 , 1991	1657115
Zhang H, Yoshikawa K, Tamura K et al. Carbon-11-methionine positron emission tomography imaging of chordoma. <i>Skeletal Radiology</i> 33(9):524 -30, 2004	15483754
<i>Liver (Hepatocellular carcinoma)</i>	
Ahmadi T, Itai Y, Onaya H, Yoshioka H, Okumura T, Akine Y. CT evaluation of hepatic injury following proton beam irradiation: appearance, enhancement, and 3D size reduction pattern. <i>Journal of Computer Assisted Tomography</i> 23(5):655 -63, 1999	10524841
Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. <i>Gastroenterology</i> 127 (5 Suppl 1):S189 -93 , 2004	15508084
Chiba,T.; Tokuuye,K.; Matsuzaki,Y.; Sugahara,S.; Chuganji,Y.; Kagei,K.; Shoda,J.; Hata,M.; Abei,M.; Igaki,H.; Tanaka,N.; Akine,Y.. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. <i>Clinical Cancer Research</i> .11(10):3799.-805., 2005	15897579

<i>Citation</i>	<i>PMID</i>
Hashimoto T, Tokuuye K, Fukumitsu N et al. Repeated proton beam therapy for hepatocellular carcinoma. <i>International Journal of Radiation Oncology, Biology, Physics</i> 65 (1):196 -202 , 2006	16563656
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. <i>Cancer</i> 107 (3):591 -8 , 2006	16804931
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for aged patients with hepatocellular carcinoma. <i>International Journal of Radiation Oncology, Biology, Physics</i> 69 (3):805 -12, 2007	17524568
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis. <i>Strahlentherapie und Onkologie</i> 182 (12):713 -20 , 2006	17149578
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. <i>Cancer</i> 104 (4):794 -801 , 2005	15981284
Kato H, Tsujii H, Miyamoto T et al. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis. <i>International Journal of Radiation Oncology, Biology, Physics</i> 59 (5):1468 -76 , 2004	15275734
Kawashima M, Furuse J, Nishio T et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. <i>Journal of Clinical Oncology</i> 23(9):1839 -46, 2005	15774777
Matsuzaki Y, Osuga T, Saito Y et al. A new, effective, and safe therapeutic option using proton irradiation for hepatocellular carcinoma. <i>Gastroenterology</i> 106 (4):1032 -41 , 1994	7511552
Niizawa G, Ikegami T, Matsuzaki Y et al. Monitoring of hepatocellular carcinoma, following proton radiotherapy, with contrast-enhanced color Doppler ultrasonography. <i>Journal of Gastroenterology</i> 40 (3):283 -90 , 2005	15830288
Tsuji H, Okumura T, Maruhashi A et al. [Dose-volume histogram analysis of patients with hepatocellular carcinoma regarding changes in liver function after proton therapy]. [Japanese]. <i>Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica</i> 55 (5):322 -8 , 1995	7784153
<i>Lung</i>	
Bonnet RB, Bush D, Cheek GA et al. Effects of proton and combined proton/photon beam radiation on pulmonary function in patients with resectable but medically inoperable non-small cell lung cancer. <i>Chest</i> 120 (6):1803 -10, 2001	11742905
Bush DA, Dunbar RD, Bonnet R, Slater JD, Cheek GA, Slater JM. Pulmonary injury from proton and conventional radiotherapy as revealed by CT. <i>AJR American Journal of Roentgenology</i> 172 (3):735 -9, 1999	10063871
Bush DA, Slater JD, Bonnet R et al. Proton-beam radiotherapy for early-stage lung cancer. <i>Chest</i> 116 (5):1313 -9, 1999	10559093
Bush DA, Slater JD, Shin BB, Cheek G, Miller DW, Slater JM. Hypofractionated proton beam radiotherapy for stage I lung cancer. <i>Chest</i> 126 (4):1198 -203 , 2004	15486383
Hata M, Tokuuye K, Kagei K et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. <i>International Journal of Radiation Oncology, Biology, Physics</i> 68(3):786 -93 , 2007	17379439
Homma T, Ohtsu I, Tomioka S, Inoue M, Hasegawa S, Miyamoto T. [Quantitative analysis of pulmonary functional damage due to heavy ion particle irradiation therapy for lung cancer]. [Japanese]. <i>Nihon Kokyuki Gakkai Zasshi</i> 37 (2):97 -101 , 1999	10214036
Kadono K, Homma T, Kamahara K et al. Effect of heavy-ion radiotherapy on pulmonary function in stage I non-small cell lung cancer patients. <i>Chest</i> 122 (6):1925 -32 , 2002	12475828

<i>Citation</i>	<i>PMID</i>
Koto M, Miyamoto T, Yamamoto N, Nishimura H, Yamada S, Tsujii H. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy.[see comment]. <i>Radiotherapy & Oncology</i> 71(2):147 -56 , 2004	15110447
Miyamoto 2007 (no record of UI number in file)	17903054
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Schulte RW, Slater JD, Rossi CJ, Jr., Slater JM. Value and perspectives of proton radiation therapy for limited stage prostate cancer. <i>Strahlentherapie und Onkologie</i> 176(1):3-8, 2000	10650829
Shipley WU, Tepper JE, Prout GR, Jr. et al. Proton radiation as boost therapy for localized prostatic carcinoma. <i>JAMA</i> 241 (18):1912 -5, 1979	107338
Shipley WU, Verhey LJ, Munzenrider JE et al. Advanced prostate cancer: the results of a randomized comparative trial of high dose irradiation boosting with conformal protons compared with conventional dose irradiation using photons alone.[see comment]. <i>International Journal of Radiation Oncology, Biology, Physics</i> 32(1):3-12, 1995	7721636
Slater JD, Yonemoto LT, Rossi CJ, Jr. et al. Conformal proton therapy for prostate carcinoma. <i>International Journal of Radiation Oncology, Biology, Physics</i> 42 (2):299-304, 1998	9788407
Slater JD, Rossi CJ, Jr., Yonemoto LT et al. Conformal proton therapy for early-stage prostate cancer. <i>Urology</i> 53 (5):978 -84 , 1999	10223493
Slater JD, Rossi CJ, Jr., Yonemoto LT et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. <i>International Journal of Radiation Oncology, Biology, Physics</i> 59(2):348 -52, 2004	15145147
Tsuji H, Yanagi T, Ishikawa H et al. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. <i>International Journal of Radiation Oncology, Biology, Physics</i> 63(4):1153-60, 2005	15990247
Zietman AL, DeSilvio ML, Slater JD et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial.[see comment]. <i>JAMA</i> 294 (10):1233 -9, 2005	16160131
<i>Spine</i>	
Castro JR, Collier JM, Petti PL et al. Charged particle radiotherapy for lesions encircling the brain stem or spinal cord. <i>International Journal of Radiation Oncology, Biology, Physics</i> 17(3):477-84, 1989	2506156
Fitzek MM, Thornton AF, Rabinov JD et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. <i>Journal of Neurosurgery</i> 91 (2):251 -60, 1999	10433313
Hug EB, Fitzek MM, Liebsch NJ, Munzenrider JE. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. <i>International Journal of Radiation Oncology, Biology, Physics</i> 31 (3):467 -76 , 1995	7852108
Imai R, Kamada T, Tsuji H et al. Carbon ion radiotherapy for unresectable sacral chordomas. <i>Clinical Cancer Research</i> 10(17):5741 -6, 2004	15355901
Marucci L, Niemierko A, Liebsch NJ, Aboubaker F, Liu MC, Munzenrider JE. Spinal cord tolerance to high-dose fractionated 3D conformal proton-photon irradiation as evaluated by equivalent uniform dose and dose volume histogram analysis. <i>International Journal of Radiation Oncology, Biology, Physics</i> 59 (2):551 -5, 2004	15145175
Nowakowski VA, Castro JR, Petti PL et al. Charged particle radiotherapy of paraspinal tumors. <i>International Journal of Radiation Oncology, Biology, Physics</i> 22(2):295-303, 1992	1740393
Park L, Delaney TF, Liebsch NJ et al. Sacral chordomas: Impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. <i>International Journal of Radiation Oncology, Biology, Physics</i> 65 (5):1514 -21, 2006	16757128

<i>Citation</i>	<i>PMID</i>
Rutz HP, Weber DC, Sugahara S et al. Extracranial chordoma: Outcome in patients treated with function-preserving surgery followed by spot-scanning proton beam irradiation. <i>International Journal of Radiation Oncology, Biology, Physics</i> 67(2):512-20, 2007	17084540
Schoenthaler R, Castro JR, Petti PL, Baken-Brown K, Phillips TL. Charged particle irradiation of sacral chordomas. <i>International Journal of Radiation Oncology, Biology, Physics</i> 26 (2):291 -8 , 1993	8491686
<i>Uterus (cervix and corpus)</i>	
Arimoto T, Kitagawa T, Tsujii H, Ohhara K. High-energy proton beam radiation therapy for gynecologic malignancies. Potential of proton beam as an alternative to brachytherapy. <i>Cancer</i> 68(1):79 -83, 1991	1904794
Kagei K, Tokuyue K, Okumura T et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. <i>International Journal of Radiation Oncology, Biology, Physics</i> 55(5):1265-71, 2003	12654436
Kato S, Ohno T, Tsujii H et al. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. <i>International Journal of Radiation Oncology, Biology, Physics</i> 65(2):388-97, 2006	16626894
Nakano T, Suzuki M, Abe A et al. The phase I/II clinical study of carbon ion therapy for cancer of the uterine cervix. <i>Cancer Journal From Scientific American</i> 5(6):362-9, 1999	10606478
Nakano T, Suzuki Y, Ohno T et al. Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia. <i>Clinical Cancer Research</i> 12(7 Pt 1):2185 -90, 2006	16609033

Appendix D. Table of excluded studies

Appendix D Table. List of excluded studies and reasons for exclusion

<i>Citation</i>	<i>PMID</i>	<i>Reason for exclusion</i>
Abrahamsen JF, Fossa SD. Long-term morbidity after curative radiotherapy for carcinoma of the bladder. A retrospective study. <i>Strahlentherapie und Onkologie</i> 166 (9):580 -3, 1990	2120783	Not eligible RT
Allen BJ, Li Y, Rizvi SM, Russell PJ. Targeted alpha therapy of prostate cancer. <i>Methods in Molecular Medicine</i> 81 :333 -57 , 2003	12725130	Not relevant
Anonymous. Special report: stereotactic radiosurgery for intracranial lesions by gamma beam, linear accelerator, and proton beam methods. <i>Tecnologica MAP Supplement</i> :26 -7 , 1999	10346748	No primary data
Archambeau JO, Bennett GW, Levine GS, Cowen R, Akanuma A. Proton radiation therapy. <i>Radiology</i> 110 (2):445 -57 , 1974	4203944	No primary data
Archambeau JO, Slater JD, Slater JM, Tangeman R. Role for proton beam irradiation in treatment of pediatric CNS malignancies. <i>International Journal of Radiation Oncology, Biology, Physics</i> 22 (2):287 -94 , 1992	1310964	No primary data
Ask A, Johansson B, Glimelius B. The potential of proton beam radiation therapy in gastrointestinal cancer. <i>Acta Oncologica</i> 44 (8):896 -903 , 2005	16332599	No primary data
Austin JP, Urie MM, Cardenosa G, Munzenrider JE. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. <i>International Journal of Radiation Oncology, Biology, Physics</i> 25 (3):439 -44 , 1993	8436522	No primary data
Austin-Seymour M, Munzenrider JE, Verhey L, Goitein M, Suit H. [Fractionated proton radiotherapy]. [Review] [23 refs] [Russian]. <i>Meditsinskaia Radiologiia</i> 32 (8):88 -94 , 1987	3041170	Publication language
Austin-Seymour M, Urie M, Munzenrider J et al. Considerations in fractionated proton radiation therapy: clinical potential and results. <i>Radiotherapy & Oncology</i> 17(1):29 -35 , 1990	2157240	No primary data
Barker FG, Butler WE, Lyons S et al. Dose-volume prediction of radiation-related complications after proton beam radiosurgery for cerebral arteriovenous malformations.[see comment]. <i>Journal of Neurosurgery</i> 99 (2):254 -63, 2003	12924697	No malignancy
Belletti S, Mensi A, Verzeletti L. Six years experience in the use of a 10 MeV microtron for radiation therapy. <i>Acta Radiologica - Oncology</i> 23(5):375 -8 , 1984	6095608	No primary data
Blomquist E, Carlsson J. Strategy for planned radiotherapy of malignant gliomas: postoperative treatment with combinations of high dose proton irradiation and tumor seeking radionuclides. <i>International Journal of Radiation Oncology, Biology, Physics</i> 22 (2):259 -63 , 1992	1310961	No primary data

Citation	PMID	Reason for exclusion
Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study. <i>Radiotherapy & Oncology</i> 68(1):1-14, 2003	12885446	Tx planning study
Brandberg Y, Damato B, Kivela T et al. The EORTC ophthalmic oncology quality of life questionnaire module (EORTC QLQ- OPT30). Development and pre-testing (Phase I-III). <i>Eye</i> 18 (3):283 -9, 2004	15004578	Not relevant
Bush DA, McAllister CJ, Loreda LN, Johnson WD, Slater JM, Slater JD. Fractionated proton beam radiotherapy for acoustic neuroma. <i>Neurosurgery</i> 50(2):270 -3; discussion 273 -5, 2002	11844261	No malignancy
Castro JR, Gademann G, Collier JM et al. [Heavy particle radiotherapy at the University of California Lawrence Berkeley Laboratory. Clinical studies by the Northern California Oncology Group]. [Review] [26 refs] [German]. <i>Strahlentherapie und Onkologie</i> 163 (1):9 -16 , 1987	3101214	No primary data
Carpentier A, Polivka M, Blanquet A, Lot G, George B. Suboccipital and cervical chordomas: the value of aggressive treatment at first presentation of the disease. <i>Journal of Neurosurgery</i> 97 (5):1070 -7 , 2002	12450028	No extractable data
Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. <i>Transactions of the American Ophthalmological Society</i> 101 :53 -6; discussion 56 -7 , 2003	14971563	Identical duplicate
Chauvel P, Iborra-Brassart N, Courdi A et al. Proton therapy in ophthalmology: status report and problems encountered. <i>Bulletin du Cancer Radiotherapie</i> 83 Suppl:215s -8s , 1996	8949783	No primary data
Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment: an audit of 1632 patients. <i>Ophthalmology</i> 111 (5):977 -83 , 2004	15121377	No extractable data
Dawson DM, Dingman JF. Hazards of proton-beam pituitary irradiation. <i>New England Journal of Medicine</i> 282 (25):1434 , 1970	5445533	No malignancy
Desjardins L, Levy-Gabriel C, Lumbroso-Lerouic L et al. [Prognostic factors for malignant uveal melanoma. Retrospective study on 2,241 patients and recent contribution of monosomy-3 research]. [French]. <i>Journal Francais d Ophthalmologie</i> 29(7):741 -9, 2006	16988624	Not relevant
Dubikaitis I, Fedotova TA. [Dynamics of the bioelectrical activity of the brain in patients with intrasellar pituitary adenomas irradiated with a proton beam]. [Russian]. <i>Zhurnal Nevropatologii i Psikiatrii Imeni S - S - Korsakova</i> 85 (3):372 - 5, 1985	2986397	No malignancy
Feuvret L, Noel G, Weber DC et al. A treatment planning comparison of combined photon-proton beams versus proton beams-only for the treatment of skull base tumors. <i>International Journal of Radiation Oncology, Biology, Physics</i> 69 (3):944 -54, 2007	17889276	Tx planning study

Citation	PMID	Reason for exclusion
Fitzek M. Letter by M. Fitzek on Hocht S, Bechrakis NE, Nausner M, et al. Proton therapy of uveal melanomas in Berlin: 5 years of experience at the Hahn-Meitner Institut: in: Strahlenther Onkol 2004;180:419-24 (No. 7) (DOI 10.1007/s00066-004-1222-5).[comment]. Strahlentherapie und Onkologie 183 (1):49 ; author reply 50, 2007	17225946	No primary data
Fitzek MM, Linggood RM, Adams J, Munzenrider JE. Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at Harvard Cyclotron Laboratory and Massachusetts General Hospital. International Journal of Radiation Oncology, Biology, Physics 64 (5):1348 -54, 2006	16580494	No malignancy
Frau E, Rumen F, Noel G, Delacroix S, Habrand JL, Offret H. Low-dose proton beam therapy for circumscribed choroidal hemangiomas. Archives of Ophthalmology 122 (10):1471 -5, 2004	15477458	No malignancy
Goodman GB, Skarsgard LD, Thompson GB, Harrison R, Lam GK, Lugate C. Pion therapy at TRIUMF. Treatment results for astrocytoma grades 3 and 4: a pilot study. Radiotherapy & Oncology 17(1):21-8 , 1990	2157239	Not eligible RT
Graffman S, Brahme A, Larsson B. Proton radiotherapy with the Uppsala cyclotron. Experience and plans. Strahlentherapie 161 (12):764 -70 , 1985	3001977	No primary data
Gragoudas ES, Egan KM, Seddon JM et al. Survival of patients with metastases from uveal melanoma. Ophthalmology 98 (3):383 -9 ; discussion 390 , 1991	2023760	No primary data
Greiner R, Blattmann H, Thum P et al. Anaplastic astrocytoma and glioblastoma: pion irradiation with the dynamic conformation technique at the Swiss Institute for Nuclear Research (SIN). Radiotherapy & Oncology 17(1):37 -46 , 1990	2108474	Not eligible RT
Gridley DS, Bonnet RB, Bush DA et al. Time course of serum cytokines in patients receiving proton or combined photon/proton beam radiation for resectable but medically inoperable non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 60(3):759 -66 , 2004	15465192	Not relevant
Griffin TW, Davis R, Laramore GE et al. Mixed beam radiation therapy for unresectable squamous cell carcinomas of the head and neck: the results of a randomized RTOG study. International Journal of Radiation Oncology, Biology, Physics 10(12):2211 -5, 1984	6439699	Not eligible RT
Griffin TW, Weisberger EC, Laramore GE, Tong D, Blasko JC. Complications of combined surgery and neutron radiation therapy in patients with advanced carcinoma of the head and neck. Radiology 132 (1):177 -8 , 1979	451196	Not eligible RT
Gudjonsson O, Blomquist E, Lilja A, Ericson H, Bergstrom M, Nyberg G. Evaluation of the effect of high-energy proton irradiation treatment on meningiomas by means of ¹¹ C-L-methionine PET. European Journal of Nuclear Medicine 27 (12):1793 -9, 2000	11189942	No malignancy

Citation	PMID	Reason for exclusion
Gudjonsson O, Blomquist E, Nyberg G et al. Stereotactic irradiation of skull base meningiomas with high energy protons. <i>Acta Neurochirurgica</i> 141 (9):933 -40 , 1999	10526074	No malignancy
Harsh GR, Thornton AF, Chapman PH, Bussiere MR, Rabinov JD, Loeffler JS. Proton beam stereotactic radiosurgery of vestibular schwannomas. <i>International Journal of Radiation Oncology, Biology, Physics</i> 54(1):35 -44 , 2002	12182972	No malignancy
Heesters MA, Kamman RL, Mooyaart EL, Go KG. Localized proton spectroscopy of inoperable brain gliomas. Response to radiation therapy. <i>Journal of Neuro-Oncology</i> 17(1):27 -35 , 1993	8120569	Not eligible RT
Heimann H, Gochman R, Hellmich M, Bechrakis NE, Foerster MH. [Dry eye symptoms following retinal surgery and ocular tumour therapy]. [German]. <i>Ophthalmologie</i> 101 (11):1098 -104 , 2004	15098135	Not relevant
Heufelder J, Cordini D, Fuchs H et al. [Five years of proton therapy of eye neoplasms at the Hahn-Meitner Institute, Berlin]. [German]. <i>Zeitschrift fur Medizinische Physik</i> 14(1):64 -71, 2004	15104012	Not relevant
Hocht S, Wachtlin J, Bechrakis NE et al. Proton or photon irradiation for hemangiomas of the choroid? A retrospective comparison. <i>International Journal of Radiation Oncology, Biology, Physics</i> 66 (2):345 -51 , 2006	16887287	No malignancy
Holmberg K, Meijer AE, Harms-Ringdahl M, Lambert B. Chromosomal instability in human lymphocytes after low dose rate gamma-irradiation and delayed mitogen stimulation. <i>International Journal of Radiation Biology</i> 73 (1):21-34 , 1998	9464474	Not relevant
Hug EB, Slater JD. Proton radiation therapy for pediatric malignancies: status report. <i>Strahlentherapie und Onkologie</i> 175 Suppl 2:89 -91 , 1999	10394409	Not relevant
Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. [Review] [35 refs]. <i>Neurosurgery Clinics of North America</i> 11(4):627 -38 , 2000	11082173	No primary data
Isacsson U, Lennernas B, Grusell E, Jung B, Montelius A, Glimelius B. Comparative treatment planning between proton and x-ray therapy in esophageal cancer. <i>International Journal of Radiation Oncology, Biology, Physics</i> 41 (2):441 -50, 1998	9607363	Tx planning study
Jones DT, Schreuder AN, Symons JE et al. Status report of the NAC particle therapy programme. <i>Strahlentherapie und Onkologie</i> 175 Suppl 2:30 -2, 1999	10394392	Not relevant
Kang JH, Wilkens JJ, Oelfke U. Demonstration of scan path optimization in proton therapy. <i>Medical Physics</i> 34 (9):3457 -64 , 2007	17926947	No primary data
Kang Y, Zhang X, Chang JY et al. 4D Proton treatment planning strategy for mobile lung tumors. <i>International Journal of Radiation Oncology, Biology, Physics</i> 67 (3):906 -14, 2007	17293240	Tx planning study

Citation	PMID	Reason for exclusion
Kaplan ID, Castro JR, Phillips TL. Helium charged particle radiotherapy for meningioma: experience at UCLBL. University of California Lawrence Berkeley Laboratory. <i>Int J Radiat Oncol Biol Phys.</i> 1994 Jan 1;28(1):257-61.	8270449	No malignancy
Kaplan ID, Castro JR, Phillips TL. Helium charged particle radiotherapy for meningioma: experience at UCLBL. University of California Lawrence Berkeley Laboratory. <i>International Journal of Radiation Oncology, Biology, Physics</i> 28 (1):257 -61 , 1994	8270449	No malignancy
Keunen JE, Bleeker JC. [Eye-preserving treatment of uveal melanoma. Leidse Oogmelanoom Groep]. [Review] [26 refs] [Dutch]. <i>Nederlands Tijdschrift voor Geneeskunde</i> 141 (42):2005 -9 , 1997	9550751	Publication language
Kiseleva VN, Grigorova TM, Poidenko VK, Sorokina II. [Results of combined gamma-proton irradiation of patients with cervical cancer]. [Russian]. <i>Akusherstvo i Ginekologija</i> (2):37 -9 , 1986	3010758	Publication language
Kiseleva VN, Ruderman AI, Lebedev AI. [Prospects for using the Institute of Theoretical and Experimental Physics proton beam for treating gynecologic cancer patients]. [Russian]. <i>Voprosy Onkologii</i> 29 (6):34 -41 , 1983	6306925	Publication language
Kligerman MM, von Essen CF, Khan MK, Smith AR, Sternhagen CJ, Sala JM. Experience with pion radiotherapy. <i>Cancer</i> 43 (3):1043 -51 , 1979	371782	Not eligible RT
Kondrat'ev BV, Vinogradov VM, Shalek RA, Ialynych NN, Kopaneva MV. [Proton irradiation of the pituitary gland for alleviating pain in patients with disseminated prostate cancer]. [Russian]. <i>Voprosy Onkologii</i> 52(1):92 -4, 2006	16715713	Publication language
Konnov BA, Lebedeva NA, Potin VV, Isakov AV. [Results of the treatment of patients with prolactinoma using a high-energy proton beam]. [Russian]. <i>Akusherstvo i Ginekologija</i> (11):44 -7 , 1988	2853579	No malignancy
Koyama-Ito H, Kanai T, Minohara S, Tsuji H, Tsujii H. Carbon ion therapy for ocular melanoma: planning orthogonal two-port treatment. <i>Physics in Medicine & Biology</i> 52(17):5341 -52, 2007	17762090	Tx planning study
Krejcarek SC, Grant PE, Henson JW, Tarbell NJ, Yock TI. Physiologic and radiographic evidence of the distal edge of the proton beam in craniospinal irradiation. <i>International Journal of Radiation Oncology, Biology, Physics</i> 68(3):646 -9, 2007	17449195	Not relevant
Lee CH, Tait D, Nahum AE, Webb S. Comparison of proton therapy and conformal X-ray therapy in non-small cell lung cancer (NSCLC). <i>British Journal of Radiology</i> 72 (863):1078 -84 , 1999	10700825	Tx planning study
Lee V, Hungerford JL. Proton beam therapy for posterior pole circumscribed choroidal haemangioma. <i>Eye</i> 12 (Pt 6):925 -8 , 1998	10325987	No malignancy
Lo EH, Fabrikant JI. Delayed biologic reactions to stereotactic charged-particle radiosurgery in the human brain. <i>Stereotactic & Functional Neurosurgery</i> 56 (4):197 -212 , 1991	1808645	No malignancy

Citation	PMID	Reason for exclusion
Luu QT, Loreda LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. <i>Cancer Journal</i> 12(2):155 -9, 2006 , -Apr	16630407	No malignancy
Makarova GV, Matveev BP, Leonova NS, Ratner TG, Molchanov GV. [Initial experience with the use of the proton beam at the Institute of Theoretical and Experimental Physics to treat prostatic cancer]. [Russian]. <i>Meditssinskaia Radiologiiia</i> 32 (8):66 -70 , 1987	3041165	Publication language
Marks LB, Light KL, Hubbs JL et al. The impact of advanced technologies on treatment deviations in radiation treatment delivery. <i>International Journal of Radiation Oncology, Biology, Physics</i> 69 (5):1579 -86 , 2007	18035214	Not relevant
Minakova EI, Vasil'eva NN, Sviatukhina OV. [Single irradiation of the pituitary with a narrow beam of protons having 200 MeV of energy in generalized breast cancer]. [Russian]. <i>Meditssinskaia Radiologiiia</i> 22 (1):33-9, 1977	865251	Publication language
Miyanaga N, Akaza H, Okumura T et al. A bladder preservation regimen using intra-arterial chemotherapy and radiotherapy for invasive bladder cancer: a prospective study. <i>International Journal of Urology</i> 7 (2):41 -8 , 2000	10710246	Not relevant
Mock U, Bogner J, Georg D, Auberger T, Potter R. Comparative treatment planning on localized prostate carcinoma conformal photon- versus proton-based radiotherapy. <i>Strahlentherapie und Onkologie</i> 181 (7):448 -55 , 2005	15995838	Not relevant
Monzul' GD, Kondrat'eva AP, Ratner TG, Lisovets SP. [Proton irradiation of bone metastases]. [Russian]. <i>Meditssinskaia Radiologiiia</i> 29 (6):17-20 , 1984	6330488	Publication language
Monzul' GD, Letiagin VP, Ratner TG, Riabukhin I, Voinarevich AO. [Proton irradiation of the hypophysis and gamma therapy of multiple bone metastases in the complex treatment of breast cancer]. [Russian]. <i>Meditssinskaia Radiologiiia</i> 32 (8):49 -55 , 1987	3041161	Publication language
Monzul' GD, Riabukhin I. [Treatment of disseminated breast cancer with combined irradiation of the hypophysis by protons and zone gamma irradiation of the skeleton]. [Russian]. <i>Voprosy Onkologii</i> 36 (4):427 -33 , 1990	2161162	Publication language
Mullins ME, Barest GD, Schaefer PW, Hochberg FH, Gonzalez RG, Lev MH. Radiation necrosis versus glioma recurrence: conventional MR imaging clues to diagnosis. <i>Ajnr: American Journal of Neuroradiology</i> 26 (8):1967 -72 , 2005	16155144	Not relevant
Murray EM, Werner ID, Schmitt G et al. Neutron versus photon radiotherapy for local control in inoperable breast cancer. <i>Strahlentherapie und Onkologie</i> 181 (2):77 -81 , 2005	15702295	Not eligible RT
Noel G, Bollet MA, Calugaru V et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. <i>International Journal of Radiation Oncology, Biology, Physics</i>	16029801	No malignancy

Citation	PMID	Reason for exclusion
62 (5):1412 -22 , 2005		
Ohnishi T, Takahashi A, Yano T et al. Hyperthermic enhancement of tumour growth inhibition by accelerated carbon-ions in transplantable human esophageal cancer. International Journal of Hyperthermia 14(2):195 -202 , 1998 , - Apr	9589324	Not relevant
Paquis P, Pignol JP, Breteau N. [Radiotherapy of high grade glioma: use of fast neutrons, therapy and enhancement by neutron capture]. [French]. Neuro-Chirurgie 46(1):23-33, 2000	10790640	Not eligible RT
Pickles T, Goodman GB, Rheaume DE et al. Pion radiation for high grade astrocytoma: results of a randomized study. International Journal of Radiation Oncology, Biology, Physics 37 (3):491 -7 , 1997	9112443	Not eligible RT
Pommier P, Balosso J, Bolla M, Gerard JP. [The French project ETOILE: review of clinical data for light ion hadrontherapy]. [French]. Cancer Radiotherapie 6(6):369 -78 , 2002	12504776	Not relevant
Porter RW, Detwiler PW, Han PP, Spetzler RF. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron.[comment]. Neurosurgery 44 (2):424 -5, 1999	9932903	No malignancy
Price J, Wei WC, Chong CY. Cranial nerve damage in patients after alpha (heavy)-particle radiation to the pituitary. Ophthalmology 86 (6):1161 -72 , 1979	230438	No malignancy
Ronson BB, Schulte RW, Han KP, Loreda LN, Slater JM, Slater JD. Fractionated proton beam irradiation of pituitary adenomas. International Journal of Radiation Oncology, Biology, Physics 64 (2):425 -34 , 2006	16257131	No malignancy
Ronson BB, Yonemoto LT, Rossi CJ, Slater JM, Slater JD. Patient tolerance of rectal balloons in conformal radiation treatment of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 64 (5):1367 -70 , 2006	16488552	Not relevant
Ruderman AI, Novikova LA, Kiseleva VN. [Use of high energy protons in the combination treatment of cervix neoplasms]. [Russian]. Meditsinskaia Radiologiya 1919 ,5-12	4218881	Publication language
Schnabel K, Berberich W, Scharding B, Niewald M, Tkocz HJ, Dietz R. [Irradiation of grades III and IV astrocytomas with new types of radiation]. [Review] [32 refs] [German]. Strahlentherapie und Onkologie 162 (5):285 -90 , 1986	3012809	No primary data
Schneider U, Lomax A, Besserer J, Pemler P, Lombriser N, Kaser-Hotz B. The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 68(3):892 -7 , 2007	17459608	Not relevant

Citation	PMID	Reason for exclusion
Schneider U, Lomax A, Lombriser N. Comparative risk assessment of secondary cancer incidence after treatment of Hodgkin's disease with photon and proton radiation. <i>Radiation Research</i> 154 (4):382 -8 , 2000	11023601	Not relevant
Shibuya H, Tsujii H. The structural characteristics of radiation oncology in Japan in 2003. <i>International Journal of Radiation Oncology, Biology, Physics</i> 62 (5):1472 -6, 2005	16029809	No primary data
Studer UE, Gerber E, Zimmermann A, Kraft R, von Essen CF. Late results in patients treated with pi-mesons for bladder cancer.[see comment]. <i>Cancer</i> 71 (2):439 -47 , 1993	8422636	Not eligible RT
Suit HD, Goitein M, Munzenrider J et al. Increased efficacy of radiation therapy by use of proton beam. <i>Strahlentherapie und Onkologie</i> 166 (1):40 -4, 1990	2154047	No primary data
Taghian AG, Kozak KR, Katz A et al. Accelerated partial breast irradiation using proton beams: Initial dosimetric experience. <i>International Journal of Radiation Oncology, Biology, Physics</i> 65 (5):1404 -10, 2006	16730137	Tx planning study
Takahashi T, Mitsunashi N, Furuta M et al. Apoptosis induced by heavy ion (carbon) irradiation of two human tumours with different radiosensitivities in vivo: relative biological effectiveness (RBE) of carbon beam. <i>Anticancer Research</i> 18 (1A):253 -6, 1998 , -Feb	9568086	Tx planning study
Trofimov A, Nguyen PL, Coen JJ et al. Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. <i>International Journal of Radiation Oncology, Biology, Physics</i> 69 (2):444 -53 , 2007	17513063	Tx planning study
Tsunemoto H, Ishikawa T, Morita S, Kitagawa T, Tsujii H. Indications of particle radiation therapy in the treatment of carcinoma of the esophagus. <i>International Journal of Radiation Oncology, Biology, Physics</i> 22 (2):321 -4, 1992	1310967	No primary data
Tsunemoto H, Morita S, Ishikawa T et al. Proton therapy in Japan. <i>Radiation Research - Supplement</i> 8 :S235 -43 , 1985	3003785	No primary data
Vernimmen FJ, Harris JK, Wilson JA, Melvill R, Smit BJ, Slabbert JP. Stereotactic proton beam therapy of skull base meningiomas. <i>International Journal of Radiation Oncology, Biology, Physics</i> 49 (1):99 -105 , 2001	11163502	No malignancy
Watkins L, Khudados ES, Kaleoglu M, Revesz T, Sacares P, Crockard HA. Skull base chordomas: a review of 38 patients, 1958-88. <i>British Journal of Neurosurgery</i> 7 (3):241 -8 , 1993	8338644	Not eligible RT
Weber DC, Bogner J, Verwey J et al. Proton beam radiotherapy versus fractionated stereotactic radiotherapy for uveal melanomas: A comparative study. <i>International Journal of Radiation Oncology, Biology, Physics</i> 63(2):373 -84 , 2005	16168832	Tx planning study
Weber DC, Lomax AJ, Rutz HP et al. Spot-scanning proton radiation therapy for recurrent, residual or untreated intracranial meningiomas.[see comment]. <i>Radiotherapy & Oncology</i> 71(3):251 -8 , 2004	15172139	No malignancy

Citation	PMID	Reason for exclusion
Weber DC, Chan AW, Bussiere MR et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. <i>Neurosurgery</i> 53 (3):577 -86 ; discussion 586 -8 , 2003	12943574	No malignancy
Wittig A, Moss RL, Stecher-Rasmussen F et al. Neutron activation of patients following boron neutron capture therapy of brain tumors at the high flux reactor (HFR) Petten (EORTC Trials 11961 and 11011). <i>Strahlentherapie und Onkologie</i> 181 (12):774 -82, 2005	16362787	Not eligible RT
Woodruff KH, Castro JR, Quivey JM et al. Postmortem examination of 22 pancreatic carcinoma patients treated with helium ion irradiation. <i>Cancer</i> 53 (3):420 -5, 1984	6318947	Not relevant
Zherbin EA, Konnov BA, Mel'nikov LA, Zargarova OP, Miagkov VP. [Proton therapy: clinico-methodological aspects, treatment results]. [Russian]. <i>Meditinskaja Radiologija</i> 32 (8):17-22 , 1987	3041155	Publication language
Zografos L, Chamot L, Bercher L, Schalenbourg A, Egger E, Gailloud C. [Contribution of ultrasound biomicroscopy to conservative treatment of anterior uveal melanoma]. [French]. <i>Klinische Monatsblätter für Augenheilkunde</i> 208 ,414-417	8766068	Tx planning study
Zografos L, Egger E, Bercher L, Chamot L, Munkel G. Proton beam irradiation of choroidal hemangiomas. <i>American Journal of Ophthalmology</i> 126 (2):261 -8 , 1998	9727520	No malignancy
Zografos L, Gailloud C, Bercher L. [Irradiation treatment of choroidal hemangiomas]. [Review] [20 refs] [French]. <i>Journal Français d Ophthalmologie</i> 12 (11):797 -807 , 1989	2700992	No malignancy
Zytkovicz A, Daftari I, Phillips TL, Chuang CF, Verhey L, Petti PL. Peripheral dose in ocular treatments with CyberKnife and Gamma Knife radiosurgery compared to proton radiotherapy. <i>Physics in Medicine & Biology</i> 52(19):5957 -71, 2007	17881812	Not relevant

RT: radiotherapy; Tx: treatment

Appendix E. Table of screened case series and case reports

<i>Citation</i>	<i>PMID</i>
Bacchetti S, Bressan P, Della MG. Melanoma of the choroid above the optic disc: considerations concerning a clinical case. <i>Ophthalmologica</i> 212 Suppl 1:53 -6, 1998	9730752
Bhattacharyya N, Thornton AF, Joseph MP, Goodman ML, Amrein PC. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. <i>Archives of Otolaryngology -- Head & Neck Surgery</i> 123 (1):34 -40 , 1997	9006501
Char DH, Castro JR, Quivey JM et al. Helium ion charged particle therapy for choroidal melanoma. <i>Ophthalmology</i> 87 (6):565 -70 , 1980	7413146
Char DH, Crawford JB, Castro JR, Woodruff KH. Failure of choroidal melanoma to respond to helium ion therapy. <i>Archives of Ophthalmology</i> 101 (2):236 -41 , 1983	6824468
Chazalon-Pauleau E, Roux L, Patte JH, Pommier S, Bonnet D, Meyer F. [Conjunctival melanoma at corneoscleral limbus on primary acquired melanosis. A case report]. [French]. <i>Journal Francais d Ophthalmologie</i> 30 (8):e22 , 2007	17978670
Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. <i>Neurosurgical Focus</i> 10(3):E1 , 2001	16734401
Coppeto JR, Roberts M. Fibrosarcoma after proton-beam pituitary ablation. <i>Archives of Neurology</i> 36 (6):380 -1, 1979	454238
Croughs P, Deman C, Richard F, Vynckier S, Van OL. [Treatment of retinoblastoma using accelerated protons]. [French]. <i>Bulletin de la Societe Belge d Ophtalmologie</i> 243 :81 -5, 1992	1338776
Currier BL, Papagelopoulos PJ, Krauss WE, Unni KK, Yaszemski MJ. Total en bloc spondylectomy of C5 vertebra for chordoma. <i>Spine</i> 32 (9):E294 -9, 2007	17450062
D'Hermies F, Meyer A, Morel X et al. [Neovascular glaucoma following proton-beam therapy. Case report]. [French]. <i>Journal Francais d Ophthalmologie</i> 24 (1):95 -101 , 2001	11240479
DeVries A, Munzenrider JE, Hedley-Whyte T, Hug EB. [The role of radiotherapy in the treatment of malignant meningiomas]. [German]. <i>Strahlentherapie und Onkologie</i> 175 (2):62 -7 , 1999	10065140
Dithmar S, Diaz CE, Grossniklaus HE. Intraocular melanoma spread to regional lymph nodes: report of two cases. <i>Retina</i> 1920 ,76-79	10696752
Dziuk E, Merta A, Bocian E. Accidental irradiation of skin on hands with a proton beam of 4 MeV energy. <i>Strahlentherapie</i> 146 (6):685 -92 , 1973	4792265
Fries PD, Char DH, Crawford JB, Waterhouse W. Sympathetic ophthalmia complicating helium ion irradiation of a choroidal melanoma. <i>Archives of Ophthalmology</i> 105 (11):1561 -4, 1987	3675290
Fukumitsu N, Tokuyue K, Sugahara S et al. A patient surviving for eight years after proton and x-ray irradiation for advanced esophageal cancer. <i>Acta Oncologica</i> 45 (8):1132 -4, 2006	17118851
Gear HC, Kemp EG, Kacpersek A, Errington RD. Treatment of recurrent orbital haemangiopericytoma with surgery and proton beam therapy. <i>British Journal of Ophthalmology</i> 89 (1):123 -4, 2005	15615763
Gerber DS, Campo RV. Acute and chronic keratitis with ulceration after corneal exposure to helium ion irradiation. <i>American Journal of Ophthalmology</i> 104 (2):189 -90 , 1987	3618720
Gohongi T, Tokuyue K, Iida H et al. Concurrent proton beam radiotherapy and systemic chemotherapy for the metastatic liver tumor of gastric carcinoma: a case report. <i>Japanese Journal of Clinical Oncology</i> 35 (1):40 -4, 2005	15681604

Citation	PMID
Goodman DF, Char DH, Crawford JB, Stone RD, Castro JR. Uveal melanoma necrosis after helium ion therapy. <i>American Journal of Ophthalmology</i> 101 (6):643 -5, 1986	3717245
Gradoudas ES, Goitein M, Koehler A et al. Proton irradiation of choroidal melanomas. Preliminary results. <i>Archives of Ophthalmology</i> 96 (9):1583 -91 , 1978	99132
Graffman S, Haymaker W, Hugosson R, Jung B. High-energy protons in the postoperative treatment of malignant glioma. <i>Acta Radiologica: Therapy, Physics, Biology</i> 14(5):443 -61 , 1975	173141
Gragoudas ES, Goitein M, Koehler AM et al. Proton irradiation of small choroidal malignant melanomas. <i>American Journal of Ophthalmology</i> 83 (5):665 -73 , 1977	405869
Gragoudas ES, Carroll JM. Multiple choroidal metastasis from bronchial carcinoid treated with photocoagulation and proton beam irradiation. <i>American Journal of Ophthalmology</i> 87 (3):299 -304 , 1979	219697
Gragoudas ES, Goitein M, Verhey L, Munzenreider J, Suit HD, Koehler A. Proton beam irradiation. An alternative to enucleation for intraocular melanomas. <i>Ophthalmology</i> 87 (6):571 -81 , 1980	6251410
Grizzard WS, Torczynski E, Char DH. Helium ion charged-particle therapy for choroidal melanoma. Histopathologic findings in a successfully treated case. <i>Archives of Ophthalmology</i> 102 (4):576 -8 , 1984	6704015
Habrand IL, ustin-Seymour M, Birnbaum S et al. Neurovisual outcome following proton radiation therapy. <i>International Journal of Radiation Oncology, Biology, Physics</i> 16 (6):1601 -6 , 1989	2542198
Habrand JL, Mammar H, Ferrand R et al. Proton beam therapy (PT) in the management of CNS tumors in childhood. <i>Strahlentherapie und Onkologie</i> 175 Suppl 2:91 -4, 1999	10394410
Haimovici R, Mukai S, Schachat AP et al. Rhegmatogenous retinal detachment in eyes with uveal melanoma. <i>Retina</i> 16 (6):488 -96 , 1996	9002131
Hata M, Tokuyue K, Sugahara S et al. Proton irradiation in a single fraction for hepatocellular carcinoma patients with uncontrollable ascites. Technical considerations and results. <i>Strahlentherapie und Onkologie</i> 183 (8):411 -6, 2007	17680219
Hwang JM, Fu KK, Phillips TL. Results and prognostic factors in the retreatment of locally recurrent nasopharyngeal carcinoma. <i>International Journal of Radiation Oncology, Biology, Physics</i> 41 (5):1099 -111 , 1998	9719121
Igaki H, Tokuyue K, Takeda T et al. Sequential evaluation of hepatic functional reserve by 99mTechnetium-galactosyl human serum albumin scintigraphy after proton beam therapy: a report of three cases and a review of the literatures. [Review] [27 refs]. <i>Acta Oncologica</i> 45 (8):1102 -7 , 2006	17118846
Kaufman M, Swartz BE, Mandelkern M, Ropchan J, Gee M, Bland WH. Diagnosis of delayed cerebral radiation necrosis following proton beam therapy. <i>Archives of Neurology</i> 47 (4):474 -6 , 1990	2157383
Kincaid MC, Folberg R, Torczynski E et al. Complications after proton beam therapy for uveal malignant melanoma. A clinical and histopathologic study of five cases. <i>Ophthalmology</i> 95 (7):982 -91 , 1988	2845323
Kirsch DG, Ebb DH, Hernandez AH, Tarbell NJ. Proton radiotherapy for Hodgkin's disease in the sacrum. <i>Lancet Oncology</i> 6(7):532 -3, 2005	15992703
Koyama S, Kawanishi N, Fukutomi H et al. Advanced carcinoma of the stomach treated with definitive proton therapy. <i>American Journal of Gastroenterology</i> 85 (4):443 -7 , 1990	2158230
Liszauer AD, Brownstein S, Corriveau C, Deschenes J. A clinicopathological study of seven globes enucleated after primary radiation therapy for malignant melanoma of the choroid or ciliary body. <i>Canadian Journal of Ophthalmology</i> 25 (7):340 -4, 1990	2090338
Lovely TJ, Buchheit WA. Syringomyelia as a postoperative sequela of the resection	2011227

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Margo CE, Pautler SE. Granulomatous uveitis after treatment of a choroidal melanoma with proton-beam irradiation. <i>Retina</i> 10(2):140 -3, 1990	2402555
Mataftsi A, Zografos L, Chamot L, Schalenbourg A. [Choroidal melanoma in neurofibromatosis type 2: description of a case]. [French]. <i>Journal Francais d Ophthalmologie</i> 26 (5):477 -80 , 2003	12819605
Matsushita K, Ochiai T, Shimada H et al. The effects of carbon ion irradiation revealed by excised perforated intestines as a late morbidity for uterine cancer treatment. <i>Surgery Today</i> 36 (8):692 -700 , 2006	16865512
Mayahara H, Oda Y, Kawaguchi A et al. A case of hepatocellular carcinoma initially treated by carbon ions, followed by protons for marginal recurrence with portal thrombus. <i>Radiation Medicine</i> 23(7):513 -9, 2005	16485544
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Sudhamshu KC, Kouzu T, Matsutani S et al. Primary malignant melanoma of the esophagus treated with heavy-ion radiotherapy. <i>Journal of Clinical Gastroenterology</i> 37 (2):151 -4, 2003	12869887
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Torubarov FS, Zvereva ZF, Prikhod'ko AE. [A case of brain damage cause by high-energy proton flow]. [Russian]. <i>Zhurnal Nevrologii i Psikiatrii Imeni S S Korsakova</i> 102 (4):45 -8 , 2002	12001667
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Kozak KR, Kachnic LA, Adams J et al. Dosimetric feasibility of hypofractionated proton radiotherapy for neoadjuvant pancreatic cancer treatment. <i>International Journal of Radiation Oncology, Biology, Physics</i> 68(5):1557 -66 , 2007	17544599
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Appendix F. Centers that perform particle beam treatment (worldwide)

Appendix Table F1. Operating particle beam facilities around the world

Institute	Country	Particle	Maximum Clinical Energy (MeV)	Beam direction			First patient	N treated	Date of N treated
				H	V	Gan			
ITEP, Moscow	Russia	proton	250	Y	–	–	1969	4024	Dec-07
St.Petersburg	Russia	proton	1000	Y	–	–	1975	1327	Dec-07
PSI, Villigen	Switzerland	proton	72	Y	–	–	1984	4875	Dec-07
Dubna	Russia	proton	200***	Y	–	–	1999	402	Dec-07
Uppsala	Sweden	proton	200	Y	–	–	1989	840	Dec-07
Clatterbridge	England	proton	62	Y	–	–	1989	1701	Dec-07
Loma Linda	USA	proton	250	Y	–	Y	1990	11414	Nov-06
MPRI(2)	USA	proton	200	Y	–	–	1993	379	Dec-07
UCSF	USA	proton	60	Y	–	–	1994	920	Mar-07
Nice	France	proton	65	Y	–	–	1991	3129	Sep-06
Orsay	France	proton	200	Y	–	–	1991	4143	Dec-07
iThemba Labs	South Africa	proton	200	Y	–	–	1993	500	Dec-07
HIMAC, Chiba	Japan	ion	800/u	Y	Y	–	1994	3795	Jan-08
TRIUMF, Vancouver	Canada	proton	72	Y	–	–	1995	130	Dec-07
PSI, Villigen	Switzerland	proton**	250*	–	–	Y	1996	320	Dec-07
G.S.I. Darmstadt	Germany	ion**	430/u	Y	–	–	1997	384	Dec-07
HMI, Berlin	Germany	proton	72	Y	–	–	1998	1014	Dec-07
NCC, Kashiwa	Japan	proton	235	–	–	Y	1998	552	Dec-07
HIBMC,Hyogo	Japan	proton	230	–	–	Y	2001	1658	Dec-07
HIBMC,Hyogo	Japan	ion	320	Y	Y	–	2002	271	Dec-07
PMRC(2), Tsukuba	Japan	proton	250	–	–	Y	2001	1188	Dec-07
NPTC, MGH Boston	USA	proton	235	Y	–	Y	2001	2710	Oct-07
INFN-LNS, Catania	Italy	proton	60	Y	–	–	2002	151	Dec-07
Shizuoka	Japan	proton	235	Y	–	Y	2003	570	Dec-07
Wakasa WERC, Tsuruga	Japan	proton	200	Y	Y	–	2002	49	Dec-07
WPTC, Zibo	China	proton	230	Y	–	Y	2004	537	Dec-07
MD Anderson Cancer Center, Houston, TX	USA	proton	250	Y	–	Y	2006	527	Dec-07
FPTI, Jacksonville,	USA	proton	230	Y	–	Y	2006	360	Dec-07

Institute	Country	Particle	Maximum Clinical Energy (MeV)	Beam direction			First patient	N treated	Date of N treated
				H	V	Gan			
FL									
NCC, Ilsan	South Korea	proton	230	Y	-	Y	2007	155	Dec-07

N: number; H: horizontal; V: vertical; Gan: Gantry

* degraded beam for 1996 to 2006; dedicated 250 MeV proton beam from 2007 onwards

** with beam scanning (all others with spread beam)

*** degraded beam

Ordered by the time of treatment of the first patient.

Source: Particle Therapy Cooperative Group, URL: <http://ptcog.web.psi.ch/> (last accessed 06/16/2008).

Appendix Table F2. Particle beam facilities that are being planned around the world

Institute	Country	In construction	Particle	Maximum Clinical Energy (MeV) [Accelerator]	Treatment rooms	Gantries	Start date
RPTC, Munich	Germany	Y	proton	250 [SCC]	5	4	2008
WPE, Essen	Germany	Y	proton	230 [Cyc]	4	3	2009
Heidelberg/GSI Darmstadt	Germany	Y	proton, ion	430 [SCC]	3	1	2008
PTC, Marburg	Germany	Y	proton, ion	430 [Syn]	4	0	2010
Kiel	Germany	N	proton, ion	430 [Syn]	3	0	2012
RPTC, Koeln	Germany	N	proton	250 [SCC]	5	4	?
PSI, Villigen	Switzerland	Y	proton	250 [SCC]	3	+1	2007/08
UPenn	USA	Y	proton	230 [Cyc]	5	4	2009
Northern Illinois PT Res.Institute, W. Chicago, IL	USA	N	proton	250 [?]	4	2 or 3	2011
Med-AUSTRON	Austria	N	proton, ion	? [Syn]	3 to 4 (?)	2	?
Trento	Italy	N	proton	230 [Cyc]	2	1	2010?
CNAO, Pavia	Italy	Y	proton, ion	430 [SCC]	3 to 4	1	2009?
iThemba Labs	South Africa	N	proton	230 [SCC]	3	1	?
CPO, Orsay	France	Y	proton	230 [Cyc]	3	1	2010

Cyc: Cyclotron; N: no; SCC: Synchrocyclotron; Syn: synchrotron; Y: yes

Source: Particle Therapy Cooperative Group, URL: <http://ptcog.web.psi.ch/> (last accessed 06/16/2008).

Also, Tufts Medical Center (Boston, MA, USA) announced plans to start building a particle beam facility.

Appendix G (Summary Table)

Summary Table. Summary of the 8 items of section C per type of cancer

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Ocular							
Uveal melanoma (melanoma of the choroid, ciliary body, iris)	Ages: 35-66 Males: 20-64 Enrolled: 1975-2006 Variety of locations and sizes – metastasis a baseline and bilateral location excluded in most	11 centers 91 studies Non-comparative: • 4 P: n=50-2645 • 81 R: n=14-1922 Comparative, RCT (3): Sizes: 136-188 • Higher (70 GyE) vs lower (50 GyE) proton dose • Protons + laser TTT vs protons • He ions vs I-125 Comparative, nonRCT (7): Sizes: 56-1272 • Proton vs enucleation • Proton vs I-125 or Ru-106 • Proton vs Proton + laser TTT • He ion vs I-125	<ul style="list-style-type: none"> No details on instrumentation No details on algorithms <i>Other:</i> <ul style="list-style-type: none"> Use of tantalum markers to demarcate tumor on the sclera Specialized software (EYEPLAN) 	Protons (68), He (21), Carbon (2): <ul style="list-style-type: none"> Dose: 45-80 (majority 60-70) Fractions: 4-5 Unit dose: 13-16 Duration: 1-2 wk 	<i>Prior Tx:</i> Surgical excision (1) Proton or photon RT (1) <i>Concurrent Tx:</i> TTT (1)	Follow-up: Survival: • OS (40); CSS (37) Local control (37): • Local control, recurrence, response to Tx <i>Other (24):</i> Metastasis Eye retention Visual loss Visual acuity Tumor size	[Most studies do not explicitly distinguish acute from late] Late: <ul style="list-style-type: none"> Enucleation (secondary to complications) Neovascular glaucoma Rubeosis iridis Radiation maculopathy Radiation papillopathy Cataract Phthisis bulbi

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Head and neck							
chordoma, chondrosarcoma, or chondroid cancer	Ages: 13-66 Males: 34-73% Enrolled: 1974-2005 Various: previously treated & untreated; chordoma, chondrosarcoma, also a few meningioma, osteosarcoma, & others	8 centers 33 studies Non-comparative: • 2 P: n=37, 67 • 28 R: n=10-223 Comparative: 1 RCT(different doses): n=96	<i>Most studies report using "treatment planning system"</i>	He (1); proton (21); C (7); Ne or C or He or Si (2); ND (2) • Dose: 45-74 • Fractions: 8-57 • Unit dose: 1.4 to 4 Duration: 3-12 wk	<i>Prior Tx:</i> surgery (11); Photon (2); ND (20) <i>Concurrent Tx:</i> photon (9); surgery (5); ND (18)	Follow-up: 9-72 mo <i>Survival:</i> • OS (26); CSS (18); ND (6) <i>Local control:</i> (24); ND (9)	Acute: moderate hearing loss; gr 3 mucositis Late: brain edema, cranial nerve deficit, fat necrosis, hemiparesis, visual loss, osteitis, basilar artery injury, pituitary dysfunction, fatal complications, seizure, radiation necrosis of brain stem, radiation transaction of the cord, short-term memory loss, somnolence, depression, severe hearing loss, ↓psychomotor performance, temporal muscle fibrosis, brain ulceration, optic neuropathy, breast cancer
glial cell tumor (astrocytoma, glioblastoma multiforme)	Ages: 6-55 Males: 41-71% Enrolled: 1977-2002 Various: previously treated & untreated; astrocytoma, glioblastoma multiforme, glioma, also a few meningioma	4 centers 9 studies Non-comparative: • 2 P: n=20, 48 • 6 R: n=7-93 Comparative: 1 RCT(different doses): n=15	<i>Most studies report using "treatment planning system"</i>	Proton (7); C (1) • Dose: 54-77 • Fractions: 33-77 • Unit dose: 1.4 to 4 Duration: 7-10 wk	<i>Prior Tx:</i> chemo (2); Photon (2) <i>Concurrent Tx:</i> photon (6); surgery (3)	Follow-up: 5-39 mo <i>Survival:</i> • OS (6); CSS (5); ND (1) <i>Local control:</i> (5); ND (3)	Acute: gr 3 thrombocytopenia, gr 4 neurologic findings (minor?), gr 3 acute otitis media Late: radiation necrosis requiring surgery, seizure, cataract, pituitary deficiency, Moyamoya disease

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Other head & neck (including oropharyngeal but not ocular) tumors	Ages: 12-65 Males: 22-74% Enrolled: 1973-2005 neuroblastoma, melanoma, liposarcoma, malignant meningioma, squamous, adenocystic, neuroendocrine, mesenchymal tumor	6 centers 15 studies Non-comparative: • 3 P: n=19-36 • 11 R: n=14-152 Comparative: Non-randomized (SFRT or IMRT alone vs with carbon particles): n=63	<i>Most studies report using "treatment planning system"</i>	Proton (8); C (6) • Dose: 20-76 • Fractions: 11-45 • Unit dose: 1.4 to 4 Duration: 6-11 wk	<i>Prior Tx:</i> chemo (2); Surgery (7) <i>Concurrent Tx:</i> photon (4); surgery (1); chemo (5)	Follow-up: 12-90 mo <i>Survival:</i> • OS (13); CSS (7); ND (2) <i>Local control:</i> (13); ND (2)	Acute: phrenic nerve paralysis, hemianopsia, cognitive deficits, seizure, focal necrosis with mass effect requiring surgery, gr 3 mucositis, tongue ulceration leading to fistula, recurrent bacterial infection & difficulties in wound healing (had reconstruction of orbit with a metal implant prior to radiation Rx) Late: vocal cord paralysis, epiglottitis, brain damage & necrosis, CSF leak with meningitis, visual loss, myelitis, osteonecrosis, esophageal stenosis, paresis, memory loss, pituitary deficiency, seizure, ocular paralysis, hearing loss, cerebellar syndrome, paresis of the trigeminal nerve

Spine

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Spine & sacral cancer (chordoma (4), glioblastoma (1), others (4))	Ages: 45-66 Males: 53-86% Enrolled: 1976-2003 Various: previously treated & untreated; chordoma, chondrosarcoma, osteosarcoma, giant cell	4 centers 9 studies Non-comparative: • 1 P: n=23 • 8 R: n=14-85 Comparative: None	<ul style="list-style-type: none"> No details on instrumentation No details on algorithms <i>Other:</i> <ul style="list-style-type: none"> Specialized software (e.g., HIPLAN) 	He (1); Ne (1); proton (4); C (1); Ne & He (1); ND (2) • Dose: 23-94 • Fractions: 16-37 • Unit dose: 1.8-4.6 Duration: 4-14 wk	<i>Prior Tx:</i> surgery (3); chemo (1); Photon (2); ND (4) <i>Concurrent Tx:</i> photon (5); surgery (3); ND (2)	Follow-up: 20-65 mo <i>Survival:</i> • OS (9); CSS (4); ND (1) <i>Local control:</i> (8); ND (2)	Acute: ≥Gr 3 skin reaction Late: radiation injury leading to colostomy; brain stem, spinal cord, brachial plexus injury; visual complications; enucleation; osteonecrosis; secondary malignancy
Gastrointestinal							
Gastrointestinal cancer (esophagus (3), pancreas (2), bile duct (2), unspecified (1))	Ages: 59-74 Males: 32-87% Enrolled: 1975-1998 Various: squamous, adenocarcinoma, well & poorly differentiated	2 centers 8 studies Non-comparative: • 2 P: n=46, 94 • 3 R: n=11-68 Comparative: RCT (1): • [Pancreas] He RT vs photon RT: 49 non-RCT (2): • [Bile duct] Surgery + Photon RT vs Surgery + Proton RT: 22 • [Bile duct] Photon RT vs Proton RT: 62	<ul style="list-style-type: none"> No details on instrumentation No details on algorithms <i>Other:</i> <ul style="list-style-type: none"> Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., LBL's treatment planning system) 	He (3); proton (2); Ne & He (2) • Dose: 32-81 • Fractions: 30-32 • Unit dose: 1.8-3.5 Duration: 8-10 wk	<i>Prior Tx:</i> surgery (2); chemo (1); ND (2) <i>Concurrent Tx:</i> chemo (2); photon (2); brachy (2); ND (2)	Follow-up: 7-73 mo <i>Survival:</i> • OS (7); CSS (4); ND (1) <i>Local control:</i> (6); ND (2)	Acute: GI bleed; ≥Gr 3 esophagitis; cytopenia, fibrosis; radiation pneumonitis Late: radiation enteritis requiring surgery; esophageal ulceration requiring IV alimentation

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Liver, HCC	Ages: 60-81 Males: 54-83% Enrolled: 1985-2006 Patients ineligible for other Tx strategies	4 centers 13 studies Non-comparative • 3 P: n=24, 30, 34 • 10 R: n=12-162 Comparative • None	<ul style="list-style-type: none"> No details on instrumentation No details on algorithms <i>Other:</i> <ul style="list-style-type: none"> Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., PT-PLAN/NDOSE, CANVAS 8) 	Protons (12) & Carbon (1) <ul style="list-style-type: none"> Dose: 50-80 Fractions: 15-30 Unit dose: 2.0-9.0 Duration: 3-9 wk 	<i>Prior Tx:</i> Surgery (4) TACE (6) PEI (4) Proton RT (2) Ablation (2) Photon RT (1) None (2) ND (5) <i>Concurrent Tx:</i> TACE (2) None (7) ND (4)	Follow-up: 11-71 mo <i>Survival:</i> • OS (11); CSS (10) <i>Local control (8):</i> • local control rate <i>Other (5)</i> • response rate • metastasis	Acute: <ul style="list-style-type: none"> ↓WBC, ↓PLT ↑Total Bilirubin ↑AST/ALT Hepatic failure Late: <ul style="list-style-type: none"> Infectious biloma Common bile duct stenosis GI bleeding Hepatic failure

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Pelvis							
Prostate cancer Adenocarcinoma	Ages: 67-73 Males: 100% Enrolled: 1972-2004 Patients with T1-4 +/- regional lymphnode metastasis	5 centers 19 studies Non-comparative • 3 P: n=30-175 • 10 R: n=16-1255 Comparative, RCT: 3 (n=191-393) • Photon RT plus standard dose vs. high-dose proton boost RT • Photon RT plus photon boost RT vs. proton boost RT • Photon RT plus photon boost RT vs. proton boost RT Comparative, non-RCT: 2 (n=180-185) • Photon RT plus photon boost RT vs. proton boost RT • Watchful waiting vs. surgery vs. standalone photon RT vs. photon RT plus proton boost RT vs. standalone proton RT	<ul style="list-style-type: none"> No details on instrumentation No details on algorithms <i>Other:</i> <ul style="list-style-type: none"> Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., HIPLAN, modified MGH 3-D planning system, FOCUS-M) 	Protons (15) & Carbon (4) <ul style="list-style-type: none"> Dose: 54-80 Fractions: 20-44 Unit dose: 1.8-3.6 Duration: 5-9 wk 	<i>Prior Tx:</i> None (12) ND (7) <i>Concurrent Tx:</i> Hormonal (7) Photon RT (13)	Follow-up: 30-157 mo <i>Survival:</i> • OS (8); CSS (6) • biochemical disease-free survival (7) <i>Local control (9):</i> • local control rate <i>Other (0)</i>	Acute: <ul style="list-style-type: none"> Proctitis Urinary tract complication (unclear) Late: <ul style="list-style-type: none"> GI bleeding Cystitis, hematuria, urethral stricture, dysuria)

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Bladder cancer Transitional and/or squamous cell carcinomas	Ages: 55-72 Males: 80-87% Enrolled: 1985-1999 Various patients with size T2 or greater	1 center 3 studies Non-comparative: • 2 P: n=25, 35 • 1 R: n=15 Comparative • None	ND	Protons (add-on therapy) • Dose: 74-85 • Fractions: 24-34 • Unit dose: 1.8-3.0 • Duration: ND	<i>Prior Tx:</i> None (2), ND (1) <i>Concurrent Tx:</i> Resection + photon RT + chemotherapy	Follow-up: 21-57 mo <i>Survival:</i> • OS (3); CSS (3) <i>Local control:</i> (3): • Recurrence-free survival, local control rate <i>Other (1):</i> • Bladder conservation	Acute: None Late: Macrohematuria requiring surgery
Uterine cancer	Ages: 56-64 Males: 0% Enrolled: 1983-2005 Various: both previously treated & untreated patients	2 centers 5 studies Non-comparative: • 2 P: n=31, 44 • 2 R: n=15, 25 Comparative, non-RCT: 1 • Carbon RT vs Photon RT & brachytherapy: 49	ND	Protons (2) & Carbon (3) • Dose: 62-88 • Fractions: 24-30 • Unit dose: 1.8-4.0 Duration: 6-8 wk	<i>Prior Tx:</i> ND (5) <i>Concurrent Tx:</i> photon (2), ND (3)	Follow-up: 26-139 mo <i>Survival:</i> • OS (4); CSS (3) <i>Local control:</i> (5): • Recurrence-free survival, local control rate <i>Other (x):</i>	Acute: None Late: hemorrhagic cystitis needing surgery; intestinal perforation; fistulas (vesico-vaginal, recto-vaginal, sigmoid-vesico)
Others							
Skin cancers Bowen, oral verrucous carcinoma, squamous cell carcinoma	Ages: 73 Males: 83% Enrolled: ND Refused surgery for primary disease	1 center 1 study Non-comparative • 1 P: n=12 Comparative • None	ND	Protons • Dose: 55 • Fractions: 5 • Unit dose: 10 • Duration: 1 wk	<i>Prior Tx:</i> None <i>Concurrent Tx:</i> None	Follow-up: 49 mo <i>Survival:</i> • OS • <i>Local control:</i> • Local control rate <i>Other</i> • Response rate • Metastasis	Acute: • Skin erythema Late: • Skin ulcer • fistula

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Bone and soft tissue, sarcoma Chordoma, osteosarcoma, nerve sheath tumor, rhabdomyosarcoma, Chondrosarcoma, liposarcoma, and other types	Ages: 4-50 Males: 55-83% Enrolled: 1973-2005 Inoperable patients or metastatic disease	5 centers 6 studies Non-comparative • 14 R: n=12-2371 Comparative • None	HIPLAN software (2) Spot-scanning technology (1) ND (3) Immobilization techniques (2) ND (3)	Protons (4) & Carbon (2) • Dose: 50-69 • Fractions: 16-28 • Unit dose: 1.5-3.0 • Duration: 4-10 wk	<i>Prior Tx:</i> Chemotherapy (3) Surgery (2) None (1) ND (1) <i>Concurrent Tx:</i> Chemotherapy (2) None (2) ND (2)	Follow-up: 6-59 mo <i>Survival:</i> • OS (5); CSS (3) <i>Local control (4):</i> • local control rate <i>Other (nd)</i>	Acute: • Grade 1 or 2 • Grade 3 or 4 • Organ toxicities Late: • osteomyelitis • panhypopituitarism & cataract focal frontal lobe necrosis • Acute lymphocytic leukemia • Failed allograft secondary to infection • DVT and ureteral stenosis • Radiation recall reaction • Symptomatic subcapsular cataract • Symptomatic grade 3 brain necrosis
Lung, NSCLC Adenocarcinoma, squamous cell carcinoma, or large cell carcinoma	Ages: 71-75 Males: 41-84% Enrolled: 1983-2005 Inoperable patients or refusal of surgery Mostly stage I	4 centers 17 studies Non-comparative • 6 P: n=21-79 • 11 R: n=13-146 Comparative • None	• No details on instrumentation • No details on algorithms <i>Other:</i> • Use of iridium markers to facilitate better localization of tumor • Specialized software (e.g., HIPLAN)	Protons (8) & Carbon(9) • Dose: 51-98 • Fractions: 10-24 • Unit dose: 1.8-6.0 • Duration: 1-9 wk	<i>Prior Tx:</i> Lung resection (2) Chemotherapy (1) ND (14) <i>Concurrent Tx:</i> None (6) ND (11)	Follow-up: 6-59 mo <i>Survival:</i> • OS (13); CSS (9) <i>Local control (11):</i> • local control rate <i>Other (2)</i> • response rate • metastasis	Acute: • Pneumonitis Late: • Skin reaction • Pulmonary fibrosis • Pleural effusion

Cancer Type, Histology	Patient populations	Available study types	Instrumentation and algorithms	Characteristics of particle beam (range of means or medians) [doses in GyE]	Prior or concurrent interventions	Efficacy (number of studies reporting outcome)	Serious harms (excluding those attributed to co-interventions by authors)
Breast cancer	Ages: 46-75 Males: 0% Enrolled: 2004-2005 Lumpectomized cancers	2 centers 2 studies Non-comparative: • 2 P: both n=20 Comparative • None	<ul style="list-style-type: none"> • No details on instrumentation • No details on algorithms 	Protons <ul style="list-style-type: none"> • Dose: 32-40 • Fractions: 4-10 • Unit dose: 4.0-8.0 • Duration: 1-2 wk 	<i>Prior Tx:</i> None (2) <i>Concurrent Tx:</i> Surgery (2) Chemo/hormonal Tx (1) ND (1)	Follow-up: 12 mo <i>Survival:</i> • OS (1); CSS (0) <i>Local control (1):</i> • local control rate <i>Other (0)</i>	Acute: None Late: None