Appendices

Appendix A. Selected Internet Links

Appendix Table A1. Internet links for radiotherapy organizations

Organization	URL address
Deutsche Gesellschaft fur Radiooncologie	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/

(Accessed June 16, 2008)

Appendix Table A2. Internet links for particle beam instrumentation companies

Company	URL address
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/

(Accessed June 16, 2008)

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

Center/Institute	URL address
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/

(Accessed June 16, 2008)

Appendix B. Ovid Medline Search Strategy

ID	Search term	Citations
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

Citation	PMID
Bladder	
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 1990;81(2):251-7.	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 2006;64(5):1371-9.	16580495
Tsujii H, Akaza H, Ohtani M, et al. Preliminary results of bladder-preserving therapy with definitive radiotherapy and intraarterial infusion of chemotherapy. Strahlentherapie und Onkologie 1994;170 (9):531-7.	7940124
Bone	
Delaney TF, Park L, Goldberg SI, et al. Radiotherapy for local control of osteosarcoma. International Journal of Radiation Oncology, Biology, Physics 2005;61(2):492-8.	15667972
Kamada T, Tsujii H, Tsuji H, et al. Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas. Journal of Clinical Oncology 1920:4466-4471.	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 1986;9(6):488-93.	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 2007;67(2):497-504.	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 2007;69(3):865-71.	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 2004;10(5):1764-72.	15014030
Breast	
Bush DA, Slater JD, Garberoglio C, et al. A technique of partial breast irradiation utilizing proton beam radiotherapy: comparison with conformal x-ray therapy [see comment]. Cancer Journal 2007;13(2):114 -8.	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, Physics2006;66(3):691-8.	17011445
Gastrointestinal	
Castro JR, Saunders WM, Quivey JM, et al. Clinical problems in radiotherapy of carcinoma of the pancreas. American Journal of Clinical Oncology 1982;5(6):579-87.	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 1983;6(6):629-37.	6637875
Koyama S, Tsujii H, Yokota H, et al. Proton beam therapy for patients with esophageal carcinoma. Japanese Journal of Clinical Oncology 1994;24(3):144-53.	8007424
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. Radiology 1988;168(1):261-4.	3132732
Schoenthaler R, Phillips TL, Castro J, et al. Carcinoma of the extrahepatic bile ducts. The University of California at San Francisco experience. Annals of Surgery 1994;219(3):267-74.	8147607
Schoenthaler R, Castro JR, Halberg FE, et al. Definitive postoperative irradiation of bile duct carcinoma with charged particles and/or photons. International Journal of Radiation Oncology, Biology, Physics 1993;27(1):75-82.	8365945
Sugahara S, Tujii H, Tuji H, et al. [The value of frequent positioning of treatment field in radiotherapy of esophageal cancer] [Japanese]. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica 1992;52(9):1308-14.	1437536

Citation	PMID
Sugahara S, Tokuuye K, Okumura T, et al. Clinical results of proton beam therapy for cancer of the esophagus. International Journal of Radiation Oncology, Biology, Physics 2005;61(1):76-84.	15629597
Head and Neck	
Al-Mefty O, Borba LA. Skull base chordomas: a management challenge. Journal of Neurosurgery 1997;86(2):182-9.	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. Journal of Neurosurgery 1989;70(1):13-7.	2535872
Austin-Seymour M, Munzenrider J, Linggood R, et al. Fractionated proton radiation therapy of cranial and intracranial tumors. American Journal of Clinical Oncology 1990;13(4):327-30.	2165739
Benk V, Liebsch NJ, Munzenrider JE, et al. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. International Journal of Radiation Oncology, Biology, Physics 1995;31(3):577-81.	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. International Journal of Radiation Oncology, Biology, Physics 1988;15(3):559-65.	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]. International Journal of Radiation Oncology, Biology, Physics 1994;29(4):647-55.	8040010
Castro JR, Reimers MM. Charged particle radiotherapy of selected tumors in the head and neck. International Journal of Radiation Oncology, Biology, Physics 1988;14(4):711-20.	3350726
Castro JR, Phillips TL, Prados M, et al. Neon heavy charged particle radiotherapy of glioblastoma of the brain. International Journal of Radiation Oncology, Biology, Physics 1997;38(2):257-61.	9226311
Colli B, Al-Mefty O. Chordomas of the craniocervical junction: follow-up review and prognostic factors. Journal of Neurosurgery 2001;95(6):933-43.	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]. Strahlentherapie und Onkologie 2000;176(5):211-6.	10847117
Fagundes MA, Hug EB, Liebsch NJ, et al. Radiation therapy for chordomas of the base of skull and cervical spine: patterns of failure and outcome after relapse. International Journal of Radiation Oncology, Biology, Physics 1995;33(3):579-84.	7558946
Fitzek MM, Thornton AF, Harsh G, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial. International Journal of Radiation Oncology, Biology, Physics 2001;51(1):131-7.	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. Cancer 2002;94(10):2623-34.	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. International Journal of Radiation Oncology, Biology, Physics 1999;45(5):1117-26.	10613303
Gridley DS, Loredo LN, Slater JD, et al. Pilot evaluation of cytokine levels in patients undergoing radiotherapy for brain tumor. Cancer Detection & Prevention 1998;22(1):20-9.	9466045
Hasegawa A, Mizoe JE, Mizota A, et al. Outcomes of visual acuity in carbon ion radiotherapy: analysis of dose-volume histograms and prognostic factors. International Journal of Radiation Oncology, Biology, Physics 2006;64(2):396-401.	16182466
Hug EB, DeVries A, Thornton AF, et al. Management of atypical and malignant meningiomas: role of high-dose, 3D-conformal radiation therapy. Journal of Neuro-Oncology 2000;48(2):151-60.	11083080
Hug EB, Loredo LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base [see comment]. Journal of Neurosurgery 1999;91(3):432-9.	10470818
Hug EB, Muenter MW, Archambeau JO, et al. Conformal proton radiation therapy for pediatric low-grade astrocytomas. Strahlentherapie und Onkologie 2002;78(1):10-17.	11977386
Hug EB, Sweeney RA, Nurre PM, et al. Proton radiotherapy in management of pediatric base of skull tumors. International Journal of Radiation Oncology, Biology, Physics 2002;52(4):1017-24.	11958897

Citation	PMID
Igaki H, Tokuuye K, Okumura T, et al. Clinical results of proton beam therapy for skull base chordoma [review] [38 refs]. International Journal of Radiation Oncology, Biology, Physics 2004;60(4):1120-6.	15519783
Kishimoto R, Mizoe JE, Komatsu S, et al. MR imaging of brain injury induced by carbon ion radiotherapy for head and neck tumors. Magnetic Resonance in Medical Sciences 2005;4(4):159-64.	16543700
McAllister B, Archambeau JO, Nguyen MC, et al. Proton therapy for pediatric cranial tumors: preliminary report on treatment and disease-related morbidities. International Journal of Radiation Oncology, Biology, Physics 1997;39(2):455-60.	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. International Journal of Radiation Oncology, Biology, Physics 2007;69(2):390-6.	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]. International Journal of Radiation Oncology, Biology, Physics 2004;60(2):358-64.	15380567
Nishimura H, Ogino T, Kawashima M, et al. Proton-beam therapy for olfactory neuroblastoma. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):758-62.	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. Acta Oncologica 2005;44(7):700-8.	16227160
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]. Cancer Radiotherapie 2005;9(3):61-74.	15979920
Noel G, Feuvret L, Ferrand R, et al. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. Neurosurgery 2004;55(6):1252-60;discussion 1260-2.	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. Medical & Pediatric Oncology 2003;40(5):309-15.	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. Strahlentherapie und Onkologie 2003;179(4):241-8.	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. International Journal of Radiation Oncology, Biology, Physics 2001;51(2):392-8.	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]. Bulletin du Cancer 2002;89(7-8):713-23.	12206985
O'Connell JX, Renard LG, Liebsch NJ, et al. Base of skull chordoma. A correlative study of histologic and clinical features of 62 cases. Cancer 1994;74(8):2261-7.	7922977
Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. Archives of Otolaryngology—Head & Neck Surgery 2006;132(11):1242-9.	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. American Journal of Surgical Pathology 1999;23(11):1370-8.	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. International Journal of Radiation Oncology, Biology, Physics 1998;41(1):59-68.	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. International Journal of Radiation Oncology, Biology, Physics 2002;11(7):1339-47.	4008290
Schulz-Ertner D, Haberer T, Jakel O, et al. Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions. International Journal of Radiation Oncology, Biology, Physics 2002;53(1):36-42.	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. Radiotherapy & Oncology 2002;64(2):189-95.	12242129

Citation	PMID
Schulz-Ertner D, Karger CP, Feuerhake A, et al. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. International Journal of Radiation Oncology, Biology, Physics2007;68(2):449-57.	17363188
Schulz-Ertner D, Nikoghosyan A, Didinger B, et al. Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques. Cancer 2005;104(2):338-44.	15937907
Schulz-Ertner D, Nikoghosyan A, Didinger B, et al. Carbon ion radiation therapy for chordomas and low grade chondrosarcomas—current status of the clinical trials at GSI. Radiotherapy & Oncology 2004;73 Suppl 2:S53-6.	15971310
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. International Journal of Radiation Oncology, Biology, Physics 2003;56(2):391-8.	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. Strahlentherapie und Onkologie 2003;179(9):598-605.	14628125
Schulz-Ertner D, Nikoghosyan A, Thilmann C, et al. Results of carbon ion radiotherapy in 152 patients. International Journal of Radiation Oncology, Biology, Physics 2004;58(2):631-40.	14751537
Slater JD, ustin-Seymour M, Munzenrider J, et al. Endocrine function following high dose proton therapy for tumors of the upper clivus. International Journal of Radiation Oncology, Biology, Physics 1988;15(3):607-11.	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. International Journal of Radiation Oncology, Biology, Physics 2005;62(2):494-500.	15890592
Suit HD, Goitein M, Munzenrider J, et al. Definitive radiation therapy for chordoma and chondrosarcoma of base of skull and cervical spine. Journal of Neurosurgery 1982;56(3):377-85.	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. International Journal of Radiation Oncology, Biology, Physics 1999;45(2):351-8.	10487555
Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. Strahlentherapie und Onkologie 2004;180(2):96-101.	14762662
Weber DC, Chan AW, Lessell S, et al. Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. Radiotherapy & Oncology 2006;81(3):243-9.	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. International Journal of Radiation Oncology, Biology, Physics 2005;63(2):401-9.	16168833
Yoshii Y, Maki Y, Narushima A, et al. [Use of radiotherapy by high-energy protons in the postoperative treatment of brain tumors] [Japanese]. Neurologia Medico-Chirurgica 1986;26(3):219-26.	2426616
Yoshii Y, Takano S, Tsurushima H, et al. Normal brain damage after radiotherapy of brain tumours. Clinical Oncology (Royal College of Radiologists) 1991;3(5):278-82.	1657115
Zhang H, Yoshikawa K, Tamura K, et al. Carbon-11-methionine positron emission tomography imaging of chordoma. Skeletal Radiology 2004;33(9):524-30.	15483754
Liver (Hepatocellular carcinoma)	
Ahmadi T, Itai Y, Onaya H, et al. CT evaluation of hepatic injury following proton beam irradiation: appearance, enhancement, and 3D size reduction pattern. Journal of Computer Assisted Tomography 1999;23(5):655-63.	10524841
Bush DA, Hillebrand DJ, Slater JM, Slater JD. High-dose proton beam radiotherapy of hepatocellular carcinoma: preliminary results of a phase II trial. Gastroenterology 2004;127(5 Suppl 1):S189-93.	15508084
Chiba T, Tokuuye K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. Clinical Cancer Research 2005;11(10):3799-805.	15897579
Hashimoto T, Tokuuye K, Fukumitsu N, et al. Repeated proton beam therapy for hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics 2006;65(1):196-202.	16563656
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. Cancer 107 (3):591 -8 , 2006	16804931

Citation	PMID
Hata M, Tokuuye K, Sugahara S et al. Proton beam therapy for aged patients with hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics 69 (3):805 -12, 2007	17524568
Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma patients with severe cirrhosis. Strahlentherapie und Onkologie 2006;182(12):713-20.	17149578
Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with portal vein tumor thrombus. Cancer 2005;104(4):794-801.	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. International Journal of Radiation Oncology, Biology, Physics 2004;59(5):1468-76.	15275734
Kawashima M, Furuse J, Nishio T et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. Journal of Clinical Oncology 2005;23(9):1839-46.	15774777
Matsuzaki Y, Osuga T, Saito Y, et al. A new, effective, and safe therapeutic option using proton irradiation for hepatocellular carcinoma. Gastroenterology 1994;106(4):1032-41.	7511552
Niizawa G, Ikegami T, Matsuzaki Y, et al. Monitoring of hepatocellular carcinoma, following proton radiotherapy, with contrast-enhanced color Doppler ultrasonography. Journal of Gastroenterology 2005;40(3):283-90.	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]. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica 1995;55(5):322-8.	7784153
Lung	
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. Chest 2001;120(6):1803-10.	11742905
Bush DA, Dunbar RD, Bonnet R, et al. Pulmonary injury from proton and conventional radiotherapy as revealed by CT. AJR American Journal of Roentgenology 1999;172(3):735-9.	10063871
Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. Chest 1999;116(5):1313-9.	10559093
Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. Chest 2004;126(4):1198-203.	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. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):786-93.	17379439
Homma T, Ohtsu I, Tomioka S, et al. [Quantitative analysis of pulmonary functional damage due to heavy ion particle irradiation therapy for lung cancer] [Japanese]. Nihon Kokyuki Gakkai Zasshi 1999;37(2):97-101.	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. Chest 2002;122(6):1925-32.	12475828
Koto M, Miyamoto T, Yamamoto N, et al. Local control and recurrence of stage I non-small cell lung cancer after carbon ion radiotherapy [see comment]. Radiotherapy & Oncology 2004;71(2):147-56.	15110447
Miyamoto 2007 (no record of UI number in file)	17903054
Miyamoto T, Baba M, Yamamoto N, et al. Curative treatment of Stage I non-small-cell lung cancer with carbon ion beams using a hypofractionated regimen. International Journal of Radiation Oncology, Biology, Physics 2007;67(3):750-8.	17293232
Miyamoto T, Yamamoto N, Koto M, et al. [Heavy-ion therapy for non-small cell lung cancer] [review] [5 refs] [Japanese]. Nippon Geka Gakkai Zasshi Journal of Japan Surgical Society 2002;103(2):250-5.	11904989
Miyamoto T, Yamamoto N, Nishimura H, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer. Radiotherapy & Oncology 2003;66(2):127-40.	12648784
Miyamoto T. [Heavy ion therapy for non-small cell lung cancer--new, radical radiotherapy for advanced-age patients as an alternative to surgery] [Japanese]. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 2003;30(2):209-14.	12610868
Nihei K, Ogino T, Ishikura S, et al. High-dose proton beam therapy for Stage I non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 2006;65(1):107-11.	16458447
Nishimura H, Miyamoto T, Yamamoto N, et al. Radiographic pulmonary and pleural changes after carbon ion irradiation. International Journal of Radiation Oncology, Biology, Physics 2003;55(4):861-6.	12605963

Citation	PMID
Satoh H, Okumura T, Yamashita YT, et al. Proton irradiation for non-small cell lung cancer. Archives of Internal Medicine 1998;158(12):1379-80.	9645836
Shioyama Y, Tokuuye K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics 2003;56(1):7-13.	12694818
Eye	
Bechrakis NE, Hocht S, Martus P, et al. [Endoresection following proton beam irradiation of large uveal melanomas] [German]. Ophthalmologe 2004;101(4):370 -6.	15067418
Bercher L, Zografos L, Egger E, et al. [Treatment of exterior extension of choroid melanomas by accelerated proton beams] [French]. Klinische Monatsblatter fur Augenheilkunde 1992:440-443	1319525
Boudinet M, Berges O, Le Huerou JY, et al. Quantitative echography in the follow-up of patients treated with proton-beam irradiation for primary choroidal melanomas. Ultrasound in Medicine & Biology 2007;33(7):1046-56.	17448588
Brovkina AF, Zarubei GD. Ciliochoroidal melanomas treated with a narrow medical proton beam. Arch Ophthalmol 1986 Mar;104(3):402-4.	3006648
Castro JR, Char DH, Petti PL, et al. 15 years experience with helium ion radiotherapy for uveal melanoma. International Journal of Radiation Oncology, Biology, Physics 1997;39(5):989-96.	9392536
Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. American Journal of Ophthalmology 2003;136(1):180-2.	12834689
Char DH, Castro JR, Kroll SM, et al. Five-year follow-up of helium ion therapy for uveal melanoma. Archives of Ophthalmology 1990;108(2):209-14.	2302103
Char DH, Castro JR, Quivey JM, et al. Uveal melanoma radiation. 125I brachytherapy versus helium ion irradiation. Ophthalmology 1989;96(12):1708-15.	2695875
Char DH, Castro JR. Helium ion therapy for choroidal melanoma. Archives of Ophthalmology 1982;100(6):935-8.	7092631
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Munzenrider JE, ustin-Seymour M, Blitzer PJ, et al. Proton therapy at Harvard. Strahlentherapie 1985;161(12):756-63.	3001976
Murayama S, Fuji H, Yamashita H, et al. [Initial clinical experience of proton therapy at Shizuoka Cancer Center] [Japanese]. Nippon Igaku Hoshasen Gakkai Zasshi - Nippon Acta Radiologica 2005;65(4):424-31.	16334397
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Umebayashi Y, Uyeno K, Tsujii H, et al. Proton radiotherapy of skin carcinomas. British Journal of Dermatology 1994;130(1):88-91.	8305324
Prostate	
Akakura K, Tsujii H, Morita S, et al. Phase I/II clinical trials of carbon ion therapy for prostate cancer [erratum appears in Prostate 2004 Sep 15;61(1):103]. Prostate 2004;58(3):252-8.	14743464
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Nihei K, Ogino T, Ishikura S, et al. Phase II feasibility study of high-dose radiotherapy for prostate cancer using proton boost therapy: first clinical trial of proton beam therapy for prostate cancer in Japan. Japanese Journal of Clinical Oncology 2005;35(12):745-52.	16314345
Rossi Jr CJ, Slater JD, Yonemoto LT, et al. Influence of patient age on biochemical freedom from disease in patients undergoing conformal proton radiotherapy of organ-confined prostate cancer. Urology 2004;64(4):729-32.	15491710
Schulte RW, Slater JD, Rossi Jr CJ, et al. Value and perspectives of proton radiation therapy for limited stage prostate cancer. Strahlentherapie und Onkologie 200;176(1):3-8.	10650829
Shipley WU, Tepper JE, Prout Jr GR, et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 1979;241(18):1912-5.	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]. International Journal of Radiation Oncology, Biology, Physics 1995;32(1):3-12.	7721636
Slater JD, Yonemoto LT, Rossi Jr CJ, et al. Conformal proton therapy for prostate carcinoma. International Journal of Radiation Oncology, Biology, Physics 1998;42(2):299-304.	9788407
Slater JD, Rossi Jr CJ, Yonemoto LT, et al. Conformal proton therapy for early-stage prostate cancer. Urology 1999;53(5):978-84.	10223493
Slater JD, Rossi Jr CJ, Yonemoto LT, et al. Proton therapy for prostate cancer: the initial Loma Linda University experience. International Journal of Radiation Oncology, Biology, Physics 2004;59(2):348-52.	15145147
Tsuji H, Yanagi T, Ishikawa H, et al. Hypofractionated radiotherapy with carbon ion beams for prostate cancer. International Journal of Radiation Oncology, Biology, Physics 2005;63(4):1153-60.	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]. JAMA 2005;294(10):1233-9.	16160131
Spine	
Castro JR, Collier JM, Petti PL, et al. Charged particle radiotherapy for lesions encircling the brain stem or spinal cord. International Journal of Radiation Oncology, Biology, Physics 1989;17(3):477-84.	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. Journal of Neurosurgery 1999;91(2):251-60.	10433313
Hug EB, Fitzek MM, Liebsch NJ, et al. Locally challenging osteo- and chondrogenic tumors of the axial skeleton: results of combined proton and photon radiation therapy using three-dimensional treatment planning. International Journal of Radiation Oncology, Biology, Physics 1995;31(3):467-76.	7852108
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Marucci L, Niemierko A, Liebsch NJ, et al. Spinal cord tolerance to high-dose fractionated 3D conformal proton-photon irradiation as evaluated by equivalent uniform dose and dose volume histogram analysis. International Journal of Radiation Oncology, Biology, Physics 2004;59(2):551-5.	15145175
Nowakowski VA, Castro JR, Petti PL, et al. Charged particle radiotherapy of paraspinal tumors. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):295-303.	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. International Journal of Radiation Oncology, Biology, Physics 2006;65(5):1514-21.	16757128
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. International Journal of Radiation Oncology, Biology, Physics 2007;67(2):512-20.	17084540
Schoenthaler R, Castro JR, Petti PL, et al. Charged particle irradiation of sacral chordomas. International Journal of Radiation Oncology, Biology, Physics 1993;26(2):291-8.	8491686

Citation	PMID
Uterus (cervix and corpus)	
Arimoto T, Kitagawa T, Tsujii H, et al. High-energy proton beam radiation therapy for gynecologic malignancies. Potential of proton beam as an alternative to brachytherapy. Cancer 1991;68(1):79-83.	1904794
Kagei K, Tokuuye K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. International Journal of Radiation Oncology, Biology, Physics 2003;55(5):1265-71.	12654436
Kato S, Ohno T, Tsujii H, et al. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. International Journal of Radiation Oncology, Biology, Physics 2006;65(2):388-97.	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. Cancer Journal From Scientific American 1999;5(6):362-9.	10606478
Nakano T, Suzuki Y, Ohno T, et al. Carbon beam therapy overcomes the radiation resistance of uterine cervical cancer originating from hypoxia. Clinical Cancer Research 2006;12(7 Pt 1):2185-90.	16609033

Appendix D. Table of Excluded Studies

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

Citation	PMID	Reason for exclusion
Abrahamsen JF, Fossa SD. Long-term morbidity after curative radiotherapy for carcinoma of the bladder. A retrospective study. Strahlentherapie und Onkologie 1990;166(9):580-3.	2120783	Not eligible RT
Allen BJ, Li Y, Rizvi SM, Russell PJ. Targeted alpha therapy of prostate cancer. Methods in Molecular Medicine 2003;81:333-57.	12725130	Not relevant
Anonymous. Special report: stereotactic radiosurgery for intracranial lesions by gamma beam, linear accelerator, and proton beam methods. Tecnologica MAP Supplement 1999:26-7.	10346748	No primary data
Archambeau JO, Bennett GW, Levine GS, et al. Proton radiation therapy. Radiology 1974;110(2):445-57.	4203944	No primary data
Archambeau JO, Slater JD, Slater JM, et al. Role for proton beam irradiation in treatment of pediatric CNS malignancies. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):287-94.	1310964	No primary data
Ask A, Johansson B, Glimelius B. The potential of proton beam radiation therapy in gastrointestinal cancer. Acta Oncologica 2005;44(8):896-903.	16332599	No primary data
Austin JP, Urie MM, Cardenosa G, et al. Probable causes of recurrence in patients with chordoma and chondrosarcoma of the base of skull and cervical spine. International Journal of Radiation Oncology, Biology, Physics 1993;25(3):439-44.	8436522	No primary data
Austin-Seymour M, Munzenrider JE, Verhey L, et al. [Fractionated proton radiotherapy] [review] [23 refs] [Russian]. Meditsinskaia Radiologiia 1987;32(8):88-94.	3041170	Publication language
Austin-Seymour M, Urie M, Munzenrider J, et al. Considerations in fractionated proton radiation therapy: clinical potential and results. Radiotherapy & Oncology 1990;17(1):29-35.	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]. Journal of Neurosurgery 2003;99(2):254-63.	12924697	No malignancy
Belletti S, Mensi A, Verzeletti L. Six years experience in the use of a 10 MeV microtron for radiation therapy. Acta Radiologica - Oncology 1984;23(5):375-8.	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. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):259-63.	1310961	No primary data
Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study. Radiotherapy & Oncology 200;68(1):1-14.	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). Eye 2004;18(3):283-9.	15004578	Not relevant
Bush DA, McAllister CJ, Loredo LN, et al. Fractionated proton beam radiotherapy for acoustic neuroma. Neurosurgery 2002;50(2):270-3;discussion 273-5.	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]. Strahlentherapie und Onkologie 1987;163(1):9-16.	3101214	No primary data
Carpentier A, Polivka M, Blanquet A, et al. Suboccipital and cervical chordomas: the value of aggressive treatment at first presentation of the disease. Journal of Neurosurgery 2002;97(5):1070-7.	12450028	No extractable data

Citation	PMID	Reason for exclusion
Char DH, Bove R, Phillips TL. Laser and proton radiation to reduce uveal melanoma-associated exudative retinal detachments. Transactions of the American Ophthalmological Society 2003;101:53--56;discussion 56-57.	14971563	Identical duplicate
Chauvel P, Iborra-Brassart N, Courdi A, et al. Proton therapy in ophthalmology: status report and problems encountered. Bulletin du Cancer Radiotherapie 1996;83 Suppl:215s-8s.	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. Ophthalmology 2004;111(5):977-83.	15121377	No extractable data
Dawson DM, Dingman JF. Hazards of proton-beam pituitary irradiation. New England Journal of Medicine 1970;282(25):1434.	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]. Journal Francais d Opthalmologie 2006;29(7):741-9.	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]. Zhurnal Nevropatologii i Psikhiatrii Imeni S - S - Korsakova 1985;85(3):372-5.	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. International Journal of Radiation Oncology, Biology, Physics 2007;69(3):944-54.	17889276	Tx planning study
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(7):419-24 (DOI 10.1007/s00066-004-1222-5) [comment]. Strahlentherapie und Onkologie 2007;183(1):49;author reply 50.	17225946	No primary data
Fitzek MM, Linggood RM, Adams J, et al. 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 2006;64(5):1348-54.	16580494	No malignancy
Frau E, Rumen F, Noel G, et al. Low-dose proton beam therapy for circumscribed choroidal hemangiomas. Archives of Ophthalmology 2004;122(10):1471-5.	15477458	No malignancy
Goodman GB, Skarsgard LD, Thompson GB, et al. Pion therapy at TRIUMF. Treatment results for astrocytoma grades 3 and 4: a pilot study. Radiotherapy & Oncology 1990;17(1):21-8.	2157239	Not eligible RT
Graffman S, Brahme A, Larsson B. Proton radiotherapy with the Uppsala cyclotron. Experience and plans. Strahlentherapie 1985;161(12):764-70.	3001977	No primary data
Gragoudas ES, Egan KM, Seddon JM, et al. Survival of patients with metastases from uveal melanoma. Ophthalmology 1991;98(3):383-9;discussion 390.	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 1990;17(1):37-46.	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 2004;60(3):759-66.	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 1984;10(12):2211-5.	6439699	Not eligible RT

Citation	PMID	Reason for exclusion
Griffin TW, Weisberger EC, Laramore GE, et al. Complications of combined surgery and neutron radiation therapy in patients with advanced carcinoma of the head and neck. Radiology 1979;132(1):177-8.	451196	Not eligible RT
Gudjonsson O, Blomquist E, Lilja A, et al. Evaluation of the effect of high-energy proton irradiation treatment on meningiomas by means of 11C-L-methionine PET. European Journal of Nuclear Medicine 2000;27(12):1793-9.	11189942	No malignancy
Gudjonsson O, Blomquist E, Nyberg G, et al. Stereotactic irradiation of skull base meningiomas with high energy protons. Acta Neurochirurgica 1999;141(9):933-40.	10526074	No malignancy
Harsh GR, Thornton AF, Chapman PH, et al. Proton beam stereotactic radiosurgery of vestibular schwannomas. International Journal of Radiation Oncology, Biology, Physics 2002;54(1):35-44.	12182972	No malignancy
Heesters MA, Kamman RL, Mooyaart EL, et al. Localized proton spectroscopy of inoperable brain gliomas. Response to radiation therapy. Journal of Neuro-Oncology 1993;17(1):27-35.	8120569	Not eligible RT
Heimann H, Gochman R, Hellmich M, et al. [Dry eye symptoms following retinal surgery and ocular tumour therapy] [German]. Ophthalmologe 2004;101(11):1098-104.	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]. Zeitschrift fur Medizinische Physik 2004;14(1):64-71.	15104012	Not relevant
Hocht S, Wachtlin J, Bechrakis NE, et al. Proton or photon irradiation for hemangiomas of the choroid? A retrospective comparison. International Journal of Radiation Oncology, Biology, Physics 2006;66(2):345-51.	16887287	No malignancy
Holmberg K, Meijer AE, Harms-Ringdahl M, et al. Chromosomal instability in human lymphocytes after low dose rate gamma-irradiation and delayed mitogen stimulation. International Journal of Radiation Biology 1998;73(1):21-34.	9464474	Not relevant
Hug EB, Slater JD. Proton radiation therapy for pediatric malignancies: status report. Strahlentherapie und Onkologie 1999;175(Suppl 2):89-91.	10394409	Not relevant
Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base [review] [35 refs]. Neurosurgery Clinics of North America 2000;11(4):627-38.	11082173	No primary data
Isacsson U, Lennernas B, Grusell E, et al. Comparative treatment planning between proton and x-ray therapy in esophageal cancer. International Journal of Radiation Oncology, Biology, Physics 1998;41(2):441-50.	9607363	Tx planning study
Jones DT, Schreuder AN, Symons JE, et al. Status report of the NAC particle therapy programme. Strahlentherapie und Onkologie 1999;175(Suppl 2):30-2.	10394392	Not relevant
Kang JH, Wilkens JJ, Oelfke U. Demonstration of scan path optimization in proton therapy. Medical Physics 2007;34(9):3457-64.	17926947	No primary data
Kang Y, Zhang X, Chang JY et al. 4D Proton treatment planning strategy for mobile lung tumors. International Journal of Radiation Oncology, Biology, Physics 67 (3):906 -14, 2007	17293240	Tx planning study
Kaplan ID, Castro JR, Phillips TL. Helium charged particle radiotherapy for meningioma: experience at UCLBL. University of California Lawrence Berkeley Laboratory. Int J Radiat Oncol Biol Phys. 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. International Journal of Radiation Oncology, Biology, Physics 1994;28(1):257-61.	8270449	No malignancy

Citation	PMID	Reason for exclusion
Keunen JE, Bleeker JC. [Eye-preserving treatment of uveal melanoma. Leidse Oogmelanoom Groep] [review] [26 refs] [Dutch]. Nederlands Tijdschrift voor Geneeskunde 1997;141(42):2005-9.	9550751	Publication language
Kiseleva VN, Grigorova TM, Poidenko VK, et al. [Results of combined gamma-proton irradiation of patients with cervical cancer] [Russian]. Akusherstvo i Ginekologiia 1986;(2):37-9.	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]. Voprosy Onkologii 1983;29(6):34-41.	6306925	Publication language
Kligerman MM, von Essen CF, Khan MK, et al. Experience with pion radiotherapy. Cancer 1979;43(3):1043-51.	371782	Not eligible RT
Kondrat'ev BV, Vinogradov VM, Shalek RA, et al. [Proton irradiation of the pituitary gland for alleviating pain in patients with disseminated prostate cancer] [Russian]. Voprosy Onkologii 2006;52(1):92-4.	16715713	Publication language
Konnov BA, Lebedeva NA, Potin VV, et al. [Results of the treatment of patients with prolactinoma using a high-energy proton beam] [Russian]. Akusherstvo i Ginekologiia 1988;(11):44-7.	2853579	No malignancy
Koyama-Ito H, Kanai T, Minohara S, et al. Carbon ion therapy for ocular melanoma: planning orthogonal two-port treatment. Physics in Medicine & Biology 2007;52(17):5341-52.	17762090	Tx planning study
Krejcarek SC, Grant PE, Henson JW, et al. Physiologic and radiographic evidence of the distal edge of the proton beam in craniospinal irradiation. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):646-9.	17449195	Not relevant
Lee CH, Tait D, Nahum AE, et al. Comparison of proton therapy and conformal X-ray therapy in non-small cell lung cancer (NSCLC). British Journal of Radiology 1999;72(863):1078-84.	10700825	Tx planning study
Lee V, Hungerford JL. Proton beam therapy for posterior pole circumscribed choroidal haemangioma. Eye 1998;12(Pt 6):925-8.	10325987	No malignancy
Lo EH, Fabrikant JI. Delayed biologic reactions to stereotactic charged-particle radiosurgery in the human brain. Stereotactic & Functional Neurosurgery 1991;56(4):197-212.	1808645	No malignancy
Luu QT, Loredo LN, Archambeau JO, et al. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. Cancer Journal 2006 Apr;12(2):155-9.	16630407	No malignancy
Makarova GV, Matveev BP, Leonova NS, et al. [Initial experience with the use of the proton beam at the Institute of Theoretical and Experimental Physics to treat prostatic cancer] [Russian]. Meditsinskaia Radiologiia 1987;32(8):66-70.	3041165	Publication language
Marks LB, Light KL, Hubbs JL, et al. The impact of advanced technologies on treatment deviations in radiation treatment delivery. International Journal of Radiation Oncology, Biology, Physics 2007;69(5):1579-86.	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]. Meditsinskaia Radiologiia 1977;22(1):33-9.	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. International Journal of Urology 2000;7(2):41-8.	10710246	Not relevant
Mock U, Bogner J, Georg D, et al. Comparative treatment planning on localized prostate carcinoma conformal photon- versus proton-based radiotherapy. Strahlentherapie und Onkologie 2005;181(7):448-55.	15995838	Not relevant
Monzul' GD, Kondrat'eva AP, Ratner TG, et al. [Proton irradiation of bone metastases] [Russian]. Meditsinskaia Radiologiia 1984;29(6):17-20.	6330488	Publication language

Citation	PMID	Reason for exclusion
Monzul' GD, Letiagin VP, Ratner TG,et al. [Proton irradiation of the hypophysis and gamma therapy of multiple bone metastases in the complex treatment of breast cancer] [Russian]. Meditsinskaia Radiologiia 1987;32(8):49-55.	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]. Voprosy Onkologii 1990;36(4):427-33.	2161162	Publication language
Mullins ME, Barest GD, Schaefer PW, et al. Radiation necrosis versus glioma recurrence: conventional MR imaging clues to diagnosis. American Journal of Neuroradiology 2005;26(8):1967-72.	16155144	Not relevant
Murray EM, Werner ID, Schmitt G, et al. Neutron versus photon radiotherapy for local control in inoperable breast cancer. Strahlentherapie und Onkologie 2005;181(2):77-81.	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. International Journal of Radiation Oncology, Biology, Physics 2005;62(5):1412-22.	16029801	No malignancy
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 1998 Apr;14(2):195-202.	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 2000;46(1):23-33.	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 1997;37(3):491-7.	9112443	Not eligible RT
Pommier P, Balosso J, Bolla M, et al. [The French project ETOILE: review of clinical data for light ion hadrontherapy] [French]. Cancer Radiotherapie 2002;6(6):369-78.	12504776	Not relevant
Porter RW, Detwiler PW, Han PP, et al. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron [comment]. Neurosurgery 1999;44(2):424-5.	9932903	No malignancy
Price J, Wei WC, Chong CY. Cranial nerve damage in patients after alpha (heavy)-particle radiation to the pituitary. Ophthalmology 1979;86(6):1161-72.	230438	No malignancy
Ronson BB, Schulte RW, Han KP, et al. Fractionated proton beam irradiation of pituitary adenomas. International Journal of Radiation Oncology, Biology, Physics 2006;64(2):425-34.	16257131	No malignancy
Ronson BB, Yonemoto LT, Rossi CJ, et al. Patient tolerance of rectal balloons in conformal radiation treatment of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 2006;64(5):1367-70.	16488552	Not relevant
Ruderman AI, Novikova LA, Kiseleva VN. [Use of high energy protons in the combination treatment of cervix neoplasms] [Russian]. Meditsinskaia Radiologiia 1919:5-12.	4218881	Publication language
Schnabel K, Berberich W, Scharding B, et al. [Irradiation of grades III and IV astrocytomas with new types of radiation] [review] [32 refs] [German]. Strahlentherapie und Onkologie 1986;162(5):285-90.	3012809	No primary data
Schneider U, Lomax A, Besserer J, et al. The impact of dose escalation on secondary cancer risk after radiotherapy of prostate cancer. International Journal of Radiation Oncology, Biology, Physics 2007;68(3):892-7.	17459608	Not relevant
Schneider U, Lomax A, Lombriser N. Comparative risk assessment of secondary cancer incidence after treatment of Hodgkin's disease with photon and proton radiation. Radiation Research 2000;154(4):382-8.	11023601	Not relevant

Citation	PMID	Reason for exclusion
Shibuya H, Tsujii H. The structural characteristics of radiation oncology in Japan in 2003. International Journal of Radiation Oncology, Biology, Physics 2005;62(5):1472-6.	16029809	No primary data
Studer UE, Gerber E, Zimmermann A, et al. Late results in patients treated with pi-mesons for bladder cancer [see comment]. Cancer 1993;71(2):439-47.	8422636	Not eligible RT
Suit HD, Goitein M, Munzenrider J, et al. Increased efficacy of radiation therapy by use of proton beam. Strahlentherapie und Onkologie 1990;166(1):40-4.	2154047	No primary data
Taghian AG, Kozak KR, Katz A, et al. Accelerated partial breast irradiation using proton beams: Initial dosimetric experience. International Journal of Radiation Oncology, Biology, Physics 2006;65(5):1404-10.	16730137	Tx planning study
Takahashi T, Mitsuhashi 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. Anticancer Research 1998 Feb;18(1A):253-6.	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. International Journal of Radiation Oncology, Biology, Physics 2007;69(2):444-53.	17513063	Tx planning study
Tsunemoto H, Ishikawa T, Morita S, et al. Indications of particle radiation therapy in the treatment of carcinoma of the esophagus. International Journal of Radiation Oncology, Biology, Physics 1992;22(2):321-4.	1310967	No primary data
Tsunemoto H, Morita S, Ishikawa T, et al. Proton therapy in Japan. Radiation Research 1985;Supplement 8:S235-43.	3003785	No primary data
Vernimmen FJ, Harris JK, Wilson JA, et al. Stereotactic proton beam therapy of skull base meningiomas. International Journal of Radiation Oncology, Biology, Physics 2001;49(1):99-105.	11163502	No malignancy
Watkins L, Khudados ES, Kaleoglu M, et al. Skull base chordomas: a review of 38 patients, 1958-88. British Journal of Neurosurgery 1993;7(3):241-8.	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. International Journal of Radiation Oncology, Biology, Physics 2005;63(2):373-84.	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]. Radiotherapy & Oncology 2004;71(3):251-8.	15172139	No malignancy
Weber DC, Chan AW, Bussiere MR, et al. Proton beam radiosurgery for vestibular schwannoma: tumor control and cranial nerve toxicity. Neurosurgery 2003;53(3):577-86;discussion 586-8.	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). Strahlentherapie und Onkologie 2005;181(12):774-82.	16362787	Not eligible RT
Woodruff KH, Castro JR, Quivey JM, et al. Postmortem examination of 22 pancreatic carcinoma patients treated with helium ion irradiation. Cancer 1984;53(3):420-5.	6318947	Not relevant
Zherbin EA, Konnov BA, Mel'nikov LA, et al. [Proton therapy: clinico-methodological aspects, treatment results] [Russian]. Meditsinskaia Radiologiia 1987;32(8):17-22.	3041155	Publication language
Zografos L, Chamot L, Bercher L, et al. [Contribution of ultrasound biomicroscopy to conservative treatment of anterior uveal melanoma] [French]. Klinische Monatsblatter fur Augenheilkunde 208:414-417.	8766068	Tx planning study

Citation	PMID	Reason for exclusion
Zografos L, Egger E, Bercher L, et al. Proton beam irradiation of choroidal hemangiomas. American Journal of Ophthalmology 1998;126(2):261-8.	9727520	No malignancy
Zografos L, Gailloud C, Bercher L. [Irradiation treatment of choroidal hemangiomas] [review] [20 refs] [French]. Journal Francais d Opthalmologie 1989;12(11):797-807.	2700992	No malignancy
Zytkovicz A, Daftari I, Phillips TL, et al. Peripheral dose in ocular treatments with CyberKnife and Gamma Knife radiosurgery compared to proton radiotherapy. Physics in Medicine & Biology 2007;52(19):5957-71.	17881812	Not relevant

RT: radiotherapy; Tx: treatment

Appendix E. Table of Screened Case Series and Case Reports

Citation	PMID
Bacchetti S, Bressan P, Della MG. Melanoma of the choroid above the optic disc: considerations concerning a clinical case. Ophthalmologica 1998;212(Suppl 1):53-6.	9730752
Bhattacharyya N, Thornton AF, Joseph MP, et al. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. Archives of Otolaryngology—Head & Neck Surgery 1997;123(1):34-40.	9006501
Char DH, Castro JR, Quivey JM, et al. Helium ion charged particle therapy for choroidal melanoma. Ophthalmology 1980;87(6):565-70.	7413146
Char DH, Crawford JB, Castro JR, et al. Failure of choroidal melanoma to respond to helium ion therapy. Archives of Ophthalmology 1983;101(2):236-41.	6824468
Chazalon-Pauleau E, Roux L, Patte JH, et al. [Conjunctival melanoma at corneoscleral limbus on primary acquired melanosis. A case report] [French]. Journal Francais d Opthalmologie 2007;30(8):e22.	17978670
Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. Neurosurgical Focus 2001;10(3):E1.	16734401
Coppeto JR, Roberts M. Fibrosarcoma after proton-beam pituitary ablation. Archives of Neurology 1979;36(6):380-1.	454238
Croughs P, Deman C, Richard F, et al. Treatment of retinoblastoma using accelerated protons] [French]. Bulletin de la Societe Belge d Ophtalmologie 1992;243:81-5.	1338776
Currier BL, Papagelopoulos PJ, Krauss WE, et al. Total en bloc spondylectomy of C5 vertebra for chordoma. Spine 2007;32(9):E294-9.	17450062
D'Hermies F, Meyer A, Morel X, et al. [Neovascular glaucoma following proton-beam therapy. Case report] [French]. Journal Francais d Opthalmologie 2001;24(1):95-101.	11240479
DeVries A, Munzenrider JE, Hedley-Whyte T, et al. [The role of radiotherapy in the treatment of malignant meningiomas] [German]. Strahlentherapie und Onkologie 1999;175(2):62-7.	10065140
Dithmar S, Diaz CE, Grossniklaus HE. Intraocular melanoma spread to regional lymph nodes: report of two cases. Retina 1920:76-79.	10696752
Dziuk E, Merta A, Bocian E. Accidental irradiation of skin on hands with a proton beam of 4 MeV energy. Strahlentherapie 1973;146(6):685-92.	4792265
Fries PD, Char DH, Crawford JB, et al. Sympathetic ophthalmia complicating helium ion irradiation of a choroidal melanoma. Archives of Ophthalmology 1987;105(11):1561-4.	3675290
Fukumitsu N, Tokuuye K, Sugahara S, et al. A patient surviving for eight years after proton and x-ray irradiation for advanced esophageal cancer. Acta Oncologica 2006;45(8):1132-4.	17118851
Gear HC, Kemp EG, Kacperek A, et al. Treatment of recurrent orbital haemangiopericytoma with surgery and proton beam therapy. British Journal of Ophthalmology 2005;89(1):123-4.	15615763
Gerber DS, Campo RV. Acute and chronic keratitis with ulceration after corneal exposure to helium ion irradiation. American Journal of Ophthalmology 1987;104(2):189-90.	3618720
Gohongi T, Tokuuye K, Iida H, et al. Concurrent proton beam radiotherapy and systemic chemotherapy for the metastatic liver tumor of gastric carcinoma: a case report. Japanese Journal of Clinical Oncology 2005;35(1):40-4.	15681604
Goodman DF, Char DH, Crawford JB, et al. Uveal melanoma necrosis after helium ion therapy. American Journal of Ophthalmology 1986;101(6):643-5.	3717245
Gradoudas ES, Goitein M, Koehler A, et al. Proton irradiation of choroidal melanomas. Preliminary results. Archives of Ophthalmology 1978;96(9):1583-91.	99132
Graffman S, Haymaker W, Hugosson R, et al. High-energy protons in the postoperative treatment of malignant glioma. Acta Radiologica: Therapy, Physics, Biology 1975;14(5):443-61.	173141
Gragoudas ES, Goitein M, Koehler AM, et al. Proton irradiation of small choroidal malignant melanomas. American Journal of Ophthalmology 1977;83(5):665-73.	405869
Gragoudas ES, Carroll JM. Multiple choroidal metastasis from bronchial carcinoid treated with photocoagulation and proton beam irradiation. American Journal of Ophthalmology 1979;87(3):299-304.	219697

Citation	PMID
Gragoudas ES, Goitein M, Verhey L, et al. Proton beam irradiation. An alternative to enucleation for intraocular melanomas. Ophthalmology 1980;87(6):571-81.	6251410
Grizzard WS, Torczynski E, Char DH. Helium ion charged-particle therapy for choroidal melanoma. Histopathologic findings in a successfully treated case. Archives of Ophthalmology 1984;102(4):576-8.	6704015
Habrand IL, ustin-Seymour M, Birnbaum S, et al. Neurovisual outcome following proton radiation therapy. International Journal of Radiation Oncology, Biology, Physics 1989;16(6):1601-6.	2542198
Habrand JL, Mammar H, Ferrand R, et al. Proton beam therapy (PT) in the management of CNS tumors in childhood. Strahlentherapie und Onkologie 1999;175(Suppl 2):91-4.	10394410
Haimovici R, Mukai S, Schachat AP, et al. Rhegmatogenous retinal detachment in eyes with uveal melanoma. Retina 1996;16(6):488-96.	9002131
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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	Parti-cle	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	Switzer-land	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	Switzer-land	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

Institute	Country	Parti-cle	Maximum Clinical Energy (MeV)	Beam direction			First patient	N treated	Date of N treated
				H	V	Gan			
FPTI, Jacksonville, FL	USA	proton	230	Y	–	Y	2006	360	Dec-07
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, available at http://ptcog.web.psi.ch/. Accessed June 16, 2008.

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

Institute	Country	In construc-tion	Particle	Maximum Clinical Energy (MeV) [Accelerator]	Treat-ment 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	Switzer-land	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	2010
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, available at http://ptcog.web.psi.ch/. Accessed June 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	No details on instrumentation No details on algorithms *Other:* Use of tantalum markers to demarcate tumor on the sclera Specialized software (EYEPLAN)	Protons (68), He (21), Carbon (2): Dose: 45-80 (majority 60-70) Fractions: 4-5 Unit dose: 13-16 Duration: 1-2 wk	*Prior Tx:* Surgical excision (1) Proton or photon RT (1) Concurrent Tx: TTT (1)	Follow-up: Survival: OS (40); CSS (37) Local control (37): Local control, recurrence, response to Tx *Other (24):* Metastasis Eye retention Visual loss Visual acuity Tumor size	[Most studies do not explicitly distinguish acute from late] Late: 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	*Most studies report using "treatment planning system"*	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	*Prior Tx:* surgery (11); Photon (2); ND (20) *Concurrent Tx:* photon (9); surgery (5); ND (18)	Follow-up: 9-72 mo *Survival:* OS (26); CSS (18); ND (6) *Local control:* (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

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)
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	*Most studies report using "treatment planning system"*	Proton (7); C (1) Dose: 54-77 Fractions: 33-77 Unit dose: 1.4 to 4 Duration: 7-10 wk	*Prior Tx:* chemo (2); Photon (2) *Concurrent Tx:* photon (6); surgery (3)	Follow-up: 5-39 mo *Survival:* OS (6); CSS (5); ND (1) *Local control:* (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	*Most studies report using "treatment planning system"*	Proton (8); C (6) Dose: 20-76 Fractions: 11-45 Unit dose: 1.4 to 4 Duration: 6-11 wk	*Prior Tx:* chemo (2); Surgery (7) *Concurrent Tx:* photon (4); surgery (1); chemo (5)	Follow-up: 12-90 mo *Survival:* OS (13); CSS (7); ND (2) *Local control:* (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

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							
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	No details on instrumentation No details on algorithms *Other:* 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	*Prior Tx:* surgery (3); chemo (1); Photon (2); ND (4) *Concurrent Tx:* photon (5); surgery (3); ND (2)	Follow-up: 20-65 mo *Survival:* OS (9); CSS (4); ND (1) *Local control:* (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	No details on instrumentation No details on algorithms *Other:* 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	*Prior Tx:* surgery (2); chemo (1); ND (2) *Concurrent Tx:* chemo (2); photon (2); brachy (2); ND (2)	Follow-up: 7-73 mo *Survival:* OS (7); CSS (4); ND (1) *Local control:* (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	No details on instrumentation No details on algorithms *Other:* Use of iridium markers to facilitate better localization of tumor Specialized software (e.g., PT-PLAN/NDOSE, CANVAS 8)	Protons (12) & Carbon (1) Dose: 50-80 Fractions: 15-30 Unit dose: 2.0-9.0 Duration: 3-9 wk	*Prior Tx:* Surgery (4) TACE (6) PEI (4) Proton RT (2) Ablation (2) Photon RT (1) None (2) ND (5) *Concurrent Tx:* TACE (2) None (7) ND (4)	Follow-up: 11-71 mo *Survival:* OS (11); CSS (10) *Local control (8)*: local control rate *Other (5)* response rate metastasis	Acute: ↓WBC, ↓PLT ↑Total Bilirubin ↑AST/ALT Hepatic failure Late: 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	No details on instrumentation No details on algorithms *Other:* 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) Dose: 54-80 Fractions: 20-44 Unit dose: 1.8-3.6 Duration: 5-9 wk	*Prior Tx:* None (12) ND (7) *Concurrent Tx:* Hormonal (7) Photon RT (13)	Follow-up: 30-157 mo *Survival:* OS (8); CSS (6) biochemical disease-free survival (7) *Local control (9)*: local control rate *Other (0)*	Acute: Proctitis Urinary tract complication (unclear) Late: GI bleeding Cystitis, hematuria, urethral strincture, 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	*Prior Tx:* None (2), ND (1) *Concurrent Tx:* Resection + photon RT + chemotherapy	Follow-up: 21-57 mo *Survival:* OS (3); CSS (3) *Local control:* (3): Recurrence-free survival, local control rate *Other (1):* 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	*Prior Tx:* ND (5) *Concurrent Tx:* photon (2), ND (3)	Follow-up: 26-139 mo *Survival:* OS (4); CSS (3) *Local control:* (5): Recurrence-free survival, local control rate *Other (x):*	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	*Prior Tx:* None *Concurrent Tx:* None	Follow-up: 49 mo *Survival:* OS *Local control*: Local control rate *Other* 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	*Prior Tx:* Chemotherapy (3) Surgery (2) None (1) ND (1) *Concurrent Tx:* Chemotherapy (2) None (2) ND (2)	Follow-up: 6-59 mo *Survival:* OS (5); CSS (3) *Local control (4)*: local control rate *Other (nd)*	Acute: Grade 1 or 2 Grade 3 or 4 Organ toxicities Late: osteomyelitis panyhypopituitarism & 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 *Other:* 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	*Prior Tx:* Lung resection (2) Chemotherapy (1) ND (14) *Concurrent Tx:* None (6) ND (11)	Follow-up: 6-59 mo *Survival:* OS (13); CSS (9) *Local control (11)*: local control rate *Other (2)* 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	No details on instrumentation No details on algorithms	Protons Dose: 32-40 Fractions: 4-10 Unit dose: 4.0-8.0 Duration: 1-2 wk	*Prior Tx:* None (2) *Concurrent Tx:* Surgery (2) Chemo/hormonal Tx (1) ND (1)	Follow-up: 12 mo *Survival:* OS (1); CSS (0) *Local control (1)*: local control rate *Other (0)*	Acute: None Late: None