Chapter

Proton Cancer Therapy: Synchrotron-Based Clinical Experiences 2020 Update

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Abstract

Proton therapy is an efficient high-precision radiotherapy technique. The number of installed proton units and the available medical evidence has grown exponentially over the last 10 years. As a technology driven cancer treatment modality, specific sub-analysis based on proton beam characteristics and proton beam generators is feasible and of academic interest. International synchrotron technology-based institutions have been particularly active in evidence generating actions including the design of prospective trials, data registration projects and retrospective analysis of early clinical results. Reported evidence after 2010 of proton therapy from synchrotron based clinical results are reviewed. Physics, molecular, cellular, animal investigation and other non-clinical topics were excluded from the present analysis. The actual literature search (up to January 2020) found 192 publications, including description of results in over 29.000 patients (10 cancer sites and histological subtypes), together with some editorials, reviews or expert updated recommendations. Institutions with synchrotron-based proton therapy technology have shown consistent and reproducible results along the past decade. Bibliometrics of reported clinical experiences from 2008 to early 2020 includes 58% of publications in first quartile (1q) scientific journals classification and 13% in 2q (7% 3q, 5% 4q and 17% not specified). The distribution of reports by cancer sites and histological subtypes shown as dominant areas of clinical research and publication: lung cancer (23%), pediatric (18%), head and neck (17%), central nervous system (7%), gastrointestinal (9%), prostate (8%) and a miscellanea of neplasms including hepatocarcinoma, sarcomas and breast cancer. Over 50% of lung, pediatric, head and neck and gastrointestinal publications were 1q.

Keywords: cancer, proton therapy, synchrotron, oncology, radiotherapy

1. Background

1.1 Cancer medicine: precision, interdisciplinary and personalization

Proton beam therapy (PBT) is developing in the context of a substantial increase in the incidence of cancer, the enormous advances made in our understanding of

the biological basis and clinical implications of the disease, and the need to improve the therapeutic index: tumor control promotion and minimal clinically relevant toxicity. PBT is an accessible precision high-energy particle radiation technology, adapted to the therapeutic demands tendencies in health care and health budget of modern clinical practice [1]. Other radiotherapy (RT) solutions using hadron beams (hadron therapy) are too costly in the medium term in most clinical settings [2].

PBT is now firmly established the era of precision medicine [3]. In oncology, the principles of medicine must be well defined: Interdisciplinarity and molecular individuation. Technological excellence will only be achieved when it encompasses the different medical specialties involved in treating each individual patient. Multidisciplinary Tumor Boards (MTD) are an essential part of an efficient approach to cancer management [4]. Personalized cancer treatment is characterized by a detailed analysis of the molecular configuration and evolution of each patient's tumor (gene expression profile and nanobiology) [5]. The latest evidence suggests that tumors are probably unique to each patient, and that each tumor within the same patient (metastasis, primary site or recurrence) has its own biological pattern of progression and host adaptation pathway [6].

1.2 Vectors in radiation oncology: individualized, functional, accurate and precise therapy

RT currently helps to achieve cure over half of all patients that require this treatment; it relieves symptoms in 2 out of every 3 patients, and in general terms is a crucial therapeutic component in 3 out of every 4 cancer patients [7]. Furthermore, RT preserves organs and tissue structures (in contrast to the status resulting from radical extended surgery) and can be used in the context of radical treatment for oligometastatic and oligo-recurrent disease [8, 9]. Forecasts in healthcare systems in countries like the US suggest that by 2020, indications for RT in all types of cancer will have increased by 25%, and by 35% in the case of gastrointestinal malignancies [10].

The foregoing estimations are based on the enormous technological advances made in RT in the last 30 years. If medical advances in clinical oncology have ushered in the era of precision medicine, interdisciplinary approach in recent decades in oncological RT (which specifically uses ionizing radiation to treat cancer) have ushered in the era of accurate precise RT.

Precision RT is very efficient in promoting the local control (LC) of macroscopically identifiable cancer lesions (targeted by image-guided RT), and has an excellent therapeutic index, in other words, minimal, toxicity in normal radiation-sensitive tissue [11]. Because accurate precise RT has minimum effect on the function of the organs, systems (blood, liver, lungs, etc.) and tissues where the tumor is located, it has allowed clinicians to explore the radiobiological effects of hypofractionation, heterogeneous dose distribution within target volumes (adjusted for bioheterogeneity), and of immunomodulatory, radiation-enhancing, radiation-sensitive and radiation-protective drug interactions [12]. Finally, one of the most promising aspects of accurate precise RT is the potencial of radiation-induced immunogenicity induced by hypofractionated (>8 Gy) RT [13]. Checkpoint inhibitors and other inmunomodulators allow clinicians to explore the potential of combining systemic immunotherapy effects with precision local and atoxic RT [14].

2. Developing proton beam therapy clinical evidence

In the next decade, technological advances in PBT will bring further technological developments in precision RT into mainstream clinical practice. The dosimetric

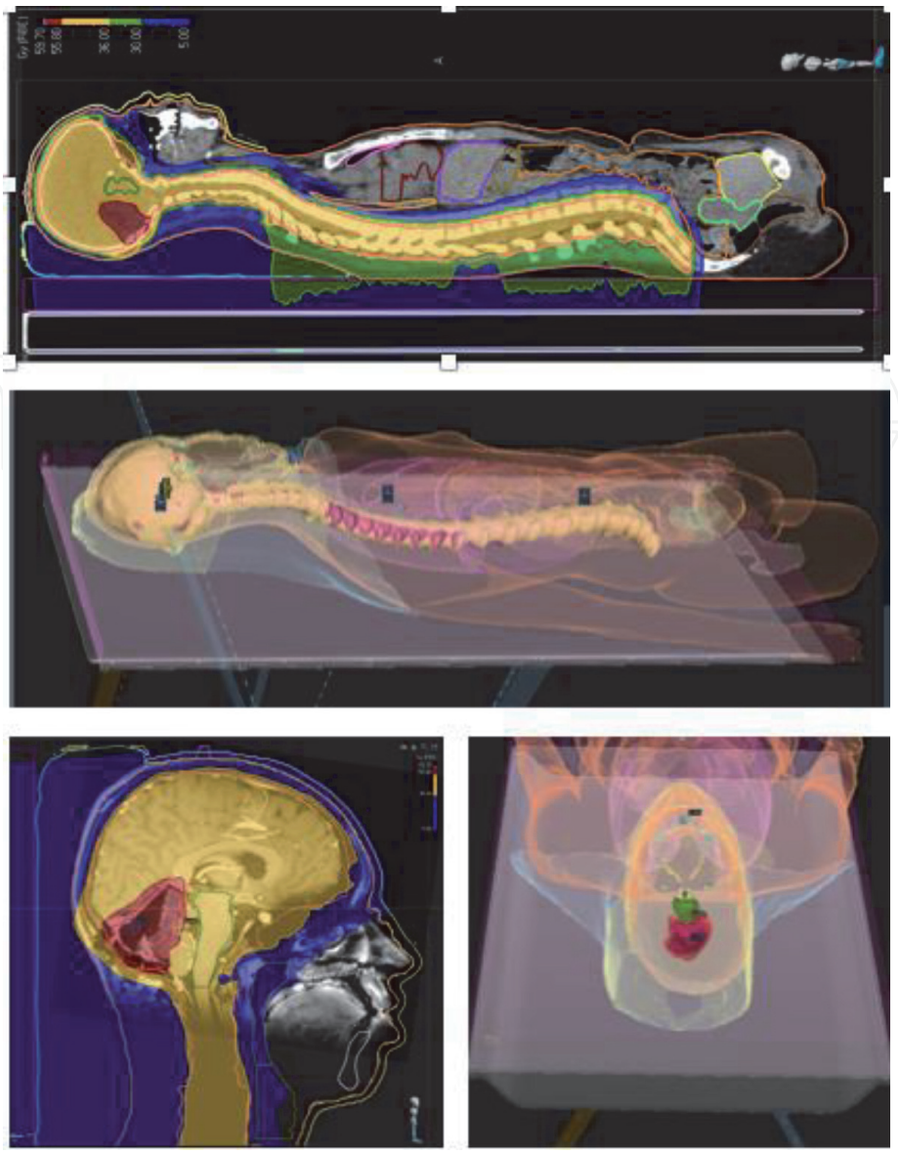

Figure 1.
Clinical practice-based example of dose distribution in a craneospinal irradiation represented in 2D and 3D images. Treatment planning implementation in PBT enhances the perception of clinical benefit expected by protecting normal anatomy from unnecessary irradiation.

precision of PBT compares favorably with photon therapy and, guided by beam homogeneity in the delivery and imaging systems for precision control (4D and quasi-real-time control), its results in clinical practice will be equivalent and reproducible (**Figure 1**).

The value of a treatment is defined as the outcomes obtained divided by the cost, measured over the entire cycle of care [15]. The clinical potential of proton cancer therapy requires sophisticated and realistic assessment of integral cost of care estimations including "costicity" (the cost of toxicity and general health-related supportive care). A collaborative effort between clinicians, patients, and policy makers is needed to design clinical trials with meaningful patient engagement. In particular, patients may help to identify and refine approaches that will lead to improved enrollment and retention in clinical trials as evidence generators sources. One crucial element in arriving at meaningful conclusions from such analyses is the need to account for the costs of managing not only acute RT toxicity but also long-term morbidities that can occur years to decades after RT is completed.

In 2016, Mishra et al. reviewed the context of developing evidence in cancer proton therapy [16]. PBT clinical trials identified from clinicaltrials.gov and the

World Health Organization International Clinical Trials Platform Registry showed a total of 122 active PBT clinical trials, with target enrollment of >42,000 patients worldwide. Ninety-six trials (79%) were interventional and 21% were observational studies. The most common PBT clinical trials focus on gastrointestinal tract tumors (21%), tumors of the central nervous system (15%), and prostate cancer (12%). Five active studies (lung, esophagus, head and neck, prostate, breast) randomize patients between protons and photons, and 3 between protons and carbon ion therapy.

The medical vision in 2020 and ahead, confirms that PBT clinical trial portfolio expands rapidly. Results of PBT studies, generated with synchrotron technology, need additional evaluation in terms of comparative effectiveness, as well as incremental effectiveness and health value offered by PBT in comparison with conventional radiation modalities among other topics of clinical relevance.

Aside from future technological improvements, PBT has already been well received in the international medical community, and is now available in more than 57 centers worldwide [17].

As in other precision RT techniques, phase III randomized clinical trials (RCTs) are not the best research setting, as they have intrinsic limitations in design and data analysis that prevent the positive findings of randomized trials investigating pharmaceuticals agents to be extrapolated to phase III studies with medical technologies. New availability of pencil-beam scanning and the consideration of new biological rationales such as avoidance of bone marrow and circulating blood radiation exposure, may be especially relevant to patients due to the central role of the immune system in cancer therapy.

3. Evolutive and consolidated clinical outcomes

Clinical results based on novel treatments need both time to mature, and a method of comparison that can define the best indications in the context of currently available accurate precise RT. Mature results from some studies recommend PBT for extreme indications in radioresistant, indolent yet highly infiltrative and extensive cancer lesions, and in patients requiring re-irradiation due to symptomatic oligo-recurrence.

The following is a summary of the clinical results of a selective review of the latest, most influential, clinical studies analyzing synchrotron-based PBT institutional outcomes. The data available generally relates to established and developmental indications, together with some comparative analysis with other RT technologies. The information was obtained from a specific literature search and systematic reviews spanning 2010–2020.

3.1 Pediatric tumors

In 2020 PBT is the radiation therapy technology of election for pediatric oncology patients. The evolution towards this practice status has been fast. A survey conducted between July 2017 and June 2018 in all proton centers treating pediatric patients in 2016 worldwide identified a total of 54 centers operating in 11 countries (Particle Therapy Co-Operative Group, PTCOG website). Among the 40 participating centers (74%), a total of 1860 patients were treated in 2016 (North America: 1205, Europe: 432, Asia: 223.

More than 30 pediatric tumor types were identified, mainly treated with curative intent. About half of the patients were treated with pencil beam scanning [18].

Pediatric cancer patients referred to proton therapy centers do benefit from expert dedicated highly specialized care both in terms of normal tissue protection to radiation exposure during treatment delivery and from early access to medical integral care and radiotherapy process (5 weeks median starting time) [19].

A critical milestone to facilitate long-term clinical outcomes research in the modern era has been achieved. The Pediatric Proton Consortium Registry (PPCR) has reported a total of 1854 patients enrolled from October 2012 until September 2017. The cohort is 55% male, 70% Caucasian, and comprised of 79% United States residents. Central nervous system (CNS) tumors were the most frequent group of diseases (61%). The most common non-CNS tumors diagnoses were: rhabdomyosarcoma (n = 191), Ewing sarcoma (n = 105), Hodgkin lymphoma (n = 66), and neuroblastoma (n = 55) (**Table 1**) [20].

3.2 Central nervous system

Radiotherapy confers survival advantages to patients with glioblastoma, medulloblastoma, germ cell, ependymoma and other intracranial neoplasms. This cost-effective and accessible treatment modality has proven efficacy in the adjuvant and definitive setting, as a first-line treatment or after prior lines of therapy. Neuro-radiation oncology has witnessed a burgeoning of new techniques, technologies and strategies that will better optimize the therapeutic ratio. Proton beam therapy (PBT) offers the potential to minimize late-onset toxicities while preserving disease-related outcomes. Multidisciplinary efforts explore synergies between the effects of radiotherapy and novel systemic therapies to tailor the delivery by molecular profile (**Table 2**) [41].

3.3 Head and neck cancer

PBT has emerged as a novel means to reduce toxicity and potentially further improve tumor control in head and neck cancer patients. The unique physical properties of charged particles allow a steep dose gradient with a reduced integral dose delivered to the patient in a proportion that can meaningfully reduce dose-related toxicity.

For the National Comprehensive Cancer Network guidelines, proton therapy is a standard of care for base of skull tumors and is an optimized option for periorbital tumors. The use of proton therapy is expanding for other cancer sites. Novel forms of proton therapy such as IMPT, and technical improvements in dose modeling, patient setup, image guidance and radiobiology, will help further enhance the benefits of proton therapy. The present cost of delivering PBT is approximately 2–3 times higher than for delivering IMRT photons in the head and neck (H&N) cancer model of health care. However, the cost difference is reduced when costs are considered over the entire cycle of care. Predictive models using comorbidity scales could defined a subpopulation of patients for whom proton therapy is likely to reduce side effects and subsequent use of health care resources (**Table 3**) [52].

3.4 Lung cancer

The call for designing and conducting "smart" proton therapy trials for lung cancer patients requires establishing clinical evidence and patient selection criteria to make proton therapy a truly personalized form of treatment. Comparative trials could focus on endpoints such as cardiac toxicity, low-dose radiation bath, and lymphopenia. The enhancement of dosimetric and biological advantages of PBT to improve clinical outcomes requires further developments in image-guided

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Haas-Kogan [21]	2018	671	Posterior fossa tumors: 57% medulloblastoma, 29% ependymoma, 14% gliomas and AT/RT*	Evaluation of brainstem toxicity	54–59.4 Gy	PB	Average rate of symptomatic brainstem toxicity 2.38%.
Mizumoto, [22]	2017	62	Head and neck (24), brain (22), body trunk (9), others (7)	Evaluation of late toxicity	10.8 to 81.2 Gy (median:50.4Gy). Standard fractionation	PB	5-, 10-, 20-year rates for grade ≥ 2 late toxicities: 18%, 35%, 45%. No tumors within irradiated field
Mizumoto, [23]	2016	343	Brain tumor (79), rhabdomyosarcoma(71), neuroblastoma(46), Ewing sarcoma (30), head and neck carcinoma(27), chordoma(14), brain stem tumor (17), cerebral arteriovenous malformation(8), others(51).	Reirradiation ± surgery± concurrent chemotherapy Evaluation of efficacy and late toxicity	10.8 to 100 Gy (median:50.4Gy). Combination PBT and photon: 24	PB ± Photon	Survival rates 1-, 3-, 5-, 10-year: 82.7%, 67.4%, 61.4%, 58.7%. Toxicity: 52 events grade ≥ 2 in 43 pts. Grade 4 in 5pts.
Buszek, [24]	2019	19	Rhabdomyosarcoma: Bladder (14) and prostate (5).	Chemotherapy ± surgical resection	36.0–50.51 Gy(RBE) (median 50.4)/1.8	PB	5-year OS and PFS: 76%. 5-year LC for tumor >5 cm 43% vs. 100% for ≤5 cm (p = 0.006). Acute grade 2 toxicity in 2 pts. (11% proctitis).
Merchant, [25]	2008	40	Optic pathway glioma (10), craniopharyngioma (10), infratentorial ependymoma (10), medulloblastoma (10).	Not reported	Not specified Comparison of toxicity between PB and photons.	PB vs. Photon	PB lower the distribution of low and intermediate (0–20, 20–40 Gy). Large difference in overall dose distribution.
Antonini, [26]	2017	39	Glioma (10), medulloblastoma (14), germ cel tumor (9), craniopharyngioma (4), other(2)	Not reported Evaluation of neurocognitive effect of PB in attention, processing speed, and executive functioning	Median, range(Gy): Focal: 50.40 (45.00–60.00) CSI: 55.80 (45.00–55.80);	PB	Focal: normal limits. CSI: difficulties in underlying component skills (i.e, processing speed)
Kahalley, [27]	2016	150	XRT: Glioma(8), medulloblastoma / PNET(28), ependymoma (13), germ cell tumor (3), other (8). PBRT: Glioma (20),	Comparison Intelligence Quotient (IQ) change after PBRT vs. XRT (60 XRT, 90 PBRT)	Median, range(Gy): Photon: 54.0 (30.6–59.4). PBRT: 54.0 (30.0–60.0)	PB vs. Photon	PBRT: no change in IQ over time. XRT: IQ declined by 1.1 points per year (P = .004).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
			medulloblastoma/ PNET (34), ependymoma (4), germ cell tumor (17), other (15)				IQ slopes did not differ between groups (P = .509
Taddei, [28]	2018	9	Medulloblastoma	Estimate reductions in projected lifetime SMN incidence and mortality if treated with proton CSI vs. photon CSI	CSI 23.4 Gy-RBE in 1.8 Gy-RBE fractions	PB vs. Photon	Ratio SMN incidence PB CSI to photon CSI: 0.56 (95% CI, 0.37 to 0.75) Ratio SMN mortality PB CSI to photon CSI: 0.64 (95% CI, 0.45 to 0.82)
Peeler, [29]	2016	34	Ependymoma (supratentorial 10, infratentorial 24)	After surgery To determine if areas of normal tissue damage were associated with increased biological dose effectiveness.	54–59.4 Gy	PB	Image changes dependence on increasing LET and dose. TD50 decreased with increasing LET = increase in biological dose effectiveness
Gunther [30]	2015	72	Ependymoma: IMRT: 21 infratentorial PBRT: 26 infratentorial	Postoperative RT ± chemotherapy before RT ± chemotherapy after RT	Median, range(Gy): IMRT 54.0 (50.4–59.4) PB 59.4 (53.0–59.4)	PB and IMRT	PBRT was associated with more frequent imaging changes(OR: 3.89, P < .024).
Sato, [31]	2017	79	Ependymoma (54 infratentorial)	Postoperative RT ± chemotherapy after RT (IMRT 38, PRT 41)	Median, range (cGy): IMRT: 5400 (5040–5940) PB: 5580 (5040–5940)	PBT and IMRT	3-year PFS rates were 60% and 82% with IMRT and PRT, respectively (P = .031)
Adesina, [32]	2019	83	Low grade glioma: Brainstem (19), cerebral hemispheres (6), thalamus (13), optic pathway/hypothalamus (29), other (16).	Surgery ± chemotherapy (IMRT 32, PBT 51)	Median, range (Gy): IMRT: 50.4 (45–59.4) PBT: 50.4 (45–54)	PB	Post-RT enlargement rates PBT vs. IMRT: HR 2.15, 95% CI 1.06–4.38, p = 0.04). RT dose >50.4Gy (RBE) > rates of PsP (HR 2.61, 95% CI 1.20–5.68, p = 0.016)
Zhang [33]	2014	17	Medulloblastoma	Surgery + chemotherapy	CSI 23.4 or 23.4 Gy (RBE) to the age specific target volume at 1.8 Gy/ fraction	PB	Proton superior outcomes (< predicted risks of 2nd cancer and cardiac mortality than photon).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Bagley, [34]	2018	18	High risk neuroblastoma: retroperitoneum/abdomen (16), thorax/mediastinum (2)	Chemotherapy + resection + autologous stem cell transplant + cis-retinoic acid ± immunotherapy	PT to primary + up to 3 MIBG-avid metastasis: - Primary sites: 21–36 Gy - Metastatic sites: 21–24 Gy	PB (1 IMPT)	2 and 5-year local control rates at primary site: 94% and 87%. 5-year overall survival (OS) 94%
McGovern, [35]	2014	31	AR/RT Tumor CNS	Surgery + Chemotherapy	Focal: 50.4GyRBE (9–54). CSI: 24–30.6 GyRBE. Tumor dose: 54 Gy (43.2–55.8)	PB	Median follow-up 24 months (3–53). PFS 20.8 months. OS 34.3 months. 16% symptoms and brainstem image changes
Grant, [36]	2015	24	Salivary gland tumor: parotid (20), submandibular (4).	Surgery ± concurrent chemotherapy (11 photons, 13 PRT)	X/E RT: 60 (54–66) PRT: 60 (56.4–66) 30 sessions	PB vs. Photons	PRT lower doses to surrounding and contralateral structures.Favorable acute toxicity and dosimetric profile.
Mizumoto, [37]	2018	55	Rhabdomyosarcoma. Histology: 18 alveolar. Localization: Head and neck (37), parameningeal (3), prostate (8), others (7).	Surgical resection ± chemotherapy	36–60 GyE (median: 50.4 GyE). Fractions: 1.8	PB	2-year OS 84.8% (95%CI 75.2–94.3%). 100%, 90.1%, 42.9% for COG low-, intermediate- and high-risk. Not specific toxicity.
Ladra, [38]	2014	54	Rhabdomyosarcoma: Orbital (12), head and neck(3), perineal/ perianal (2), biliary (1), parameningeal (24), bladder/prostate (7), extremities (3), chest/abdomen (2)	Surgical resection ± chemotherapy Dosimetric comparison of PB and IMRT	36–50.4 Gy (median 50.4 Gy)	PB vs. IMRT	Mean integral dose was 1.8 times higher for IMRT
Ladra, [39]	2014	57	Rhabdomyosarcoma: Orbital (13), head and neck (4), perineal (1), biliary (1), parameningeal (27), bladder/prostate (5), extremities (3), chest/abdomen 2, perianal 1.	Surgical resection ± chemotherapy	Radiation dose GyRBE: Median 50.4: Range 36.0–50.4		5-year EFS, OS, LC: 69%, 78%, 81%, respectively. Toxicity: Acute:13 pts. grade 3; Late: 3 pts. grade 3. No toxicities > grade 3.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Tamura, [40]	2017	26	A. Brain B. Chest C. Abdomen D. Whole CNS(medulloblastoma)	Surgery ± chemotherapy Comparison PBT to IMXT in lifetime attributable risk of radiation-induced secondary cancer (LAR)	**A:** 30.6–57.6 Gy/ 1.8 Gy. **B:** 25.2–60 Gy. /1.8–2.5Gy **C:** 25.2–72.6 Gy/ 1.8–3.3 Gy. **D:** 18–23.4 Gy/ 1.8 Gy	PB	In pts. undergone PBT LAR was lower than IMXT estimated LAR useful marker of secondary cancer induced by radiotherapy

Table 1.
Clinical experiences with synchrotron PBT in pediatric tumors (AT/RT: atypical teratoid rhabdoid tumors; OS: overall survival; PFS: progression-free survival; LC: Local control; SMN: secondary malignant neoplasms; LET: linear energy transfer; TD50; dose at which 50% of patients would experience toxicity; PsP: Pseudoprogression; EFS: event-free survival; PB: passive beam; IMRT: intensity modulated radiotherapy; IMPT: intensity modulated proton therapy; CSI craniospinal irradiation).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Bronk [42]	2018	99	Grade II-III oligodendroglioma or astrocitoma IDH mut 52%	PB(34) vs. IMRT(65) in development of pseudoprogression	50–54 RBE standard fractionation	PB	No difference in pseudoprogression rate 6 months after proton or photon therapy.
Wilkinson [43]	2016	58	Low-grade gliomas Oligodendroglioma 33% Astrocitoma 38% Mixed 29%	Evaluation of acute toxicity	50–54 RBE standard fractionation	PB	No G3 toxicity 78% G1–2 dermitis, 81% alopecia, 47% fatigue.
Amsbaugh [44]	2012	8	Primary spinal ependymomas n = 6 Grade I; n = 2 grade II.	Surgery before RT	45–54 RBE/25 fx	PB	mFT 26 months. Local control, event-free survival, and overall survival rates were all 100%
Jaramillo [45]	2019	7	Embryonal tumors with multilayered rosettes (ETMRs)	Surgery	52–56 RBE/30 fx	PB	mFT 40 months. mOS 16 months 3 pts. survived ≥36 m 5 pts. had LRF
Vatner [46]	2018	189	Medulloblastoma: 130 Ependymoma: 26 Low grade glioma: 14	CSI ± surgery ± systemic ChT	23.4 Gy/ 1.8 GyRBE	PB	-mFT 4.4y −4-y actuarial rate hormone deficency, GH, TH, ACTH and FSH/LH were 48.8%, 37.4%, 20.5%, 6.9%, and 4.1%, respectively. -Age at start of RT, time interval since treatment, and median dose to the combined hypothalamus and pituitary were correlated with increased incidence of deficiency.
Stoker [47]	2014	10	CNS tumors. 5 adults, 5 pediatric.	Compare field junction robustness and OARs in CSI IMPT vs. PSPT	N/E	IMPT	IMPT vs. PSPT (PB) lowered maximum spinal cord dose, improved spinal dose homogeneity, and reduced exposure to other OARs.
Barney [48]	2014	50	CNS tumors. 38% medulloblastoma.	Surgery + Systemic ChT	CSI 30.6 RBE + Boost 54 RBE	PB	Nausea/vomiting G2 20% Anorexia G2 10% G3 cytopenia 8%

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Brown [49]	2013	40	Medulloblastoma in adults	Surgery. EP: Acute toxicity n = 19 PBT; n = 21 photon CSI	CSI 30.6 RBE + Boost 54 RBE	PB	PBT pts. lost significantly less weight than photon pts., less nausea/vomiting, less cytopenia. Esophagitis 57% vs. 5%
Zhang [50]	2012	1	Medulloblastoma	Risk of second cancer: 3-field 6MV photon vs. 4-field PBT	CSI 23.4 RBE	PB	Lifetime risk second cancer 7.7 vs. 92%. Proton therapy confers lower predicted risk of second cancer for the pediatric medulloblastoma patient compared with photon therapy.
Bielamowicz [51]	2018	95	Medulloblastoma PBT n = 41	MRF surgery + CSI Photons vs. PBI hypothiroidism	23.4 RBE standard CSI 36–39 RBE in HR pts.	PB	Hypothiroidism: mFT PBT 3y 19% mFT photons 9y 46.3%

Table 2.
Clinical experiences in CNS tumors treated with synchrotron technology (2012–2019). OARs: organs at risk; RBE: radiobiological equivalence; CNS: central nervous system; ChT: Chemotherapy).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Blanchard [53]	2016	50 IMPT 100 IMRT	Locally advanced oropharynx cancer	IMRT vs. IMPT Neck disSection 23%	66–70 RBE/35 fx	IMPT	IMPT is associated with reduced rates of feeding tube dependency and severe weight loss
Frank [54]	2014	15	10 pts. SCC 5 pts. adenoid cystic carcinoma. Locally advanced.	NR	66–70 RBE/35 fx	IMPT	mFT: 28 m cCR: 93.3% Xerostomía G3: 1 patient Mucositis G3: 6 pts.
Bagley [55]	2020	69	Oropharingeal carcinoma stage III-IV	Xerostomia-Related QoL	70 RBE/35 fx	PB	greatest xerostomia-related QoL impairment at 6 weeks. 49% improvement after 10 wks.
Jensen [56]	2017	50 IMPT 100 IMRT	Oropharingeal carcinoma stage III-IV	Prognostic impact of leukocyte counts before and during radiotherapy. IMRT vs. IMPT	70 RBE/35 fx	IMPT	The radiotherapy type (IMRT vs. IMPT) was not associated with lymphopenia. Poor progression-free survival was associated with pretreatment leukocytosis and T status in univariate analysis, and pretreatment neutrophilia and advanced age on multivariate analysis.
Zhang [57]	2017	50 IMPT 534 IMRT	Locally advanced oropharynx cancer	IMRT vs. IMPT	66–70 RBE/35 fx	IMPT	mFT: 33.8 m Osteoradionecrosis rates: 2% IMPT, 7.7% IMRT.
Sio [58]	2016	35 IMPT 46 IMRT	Oropharyngeal Cancer Stage III-IVa.	IMRT vs. IMPT	70 RBE/35 fx	IMPT	Symptom burden was lower among the IMPT patients than among the IMRT patients during the subacute recovery phase after treatment
Gunn [59]	2016	50	Oropharingeal SCC stage III-IV	Concurrent chemo-IMPT 32% IC concurrent chemo-IMPT 30%	66–70 RBE/35 fx	IMPT	mFT: 29 m 2- year actuarial: OS 94.5%; PFS 88.6%. N = 5 recurrence. G3 toxicities: mucositis 58%; dysphagia 12%.
Ludmir [60]	2019	46	H&N alveolar rhabdomyosarcoma in children	Systemic ChT	50.4 RBE/ 25 fx.	PB	mFT: 3.9y 5-y: OS 76% PFS 57%

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
							LC: 84% Tumor size >5 cm, delayed RT after ChT and ICE increased risk.
Ludmir [61]	2018	14	H&N alveolar rhabdomyosarcoma in children 57% localized 43% N+	Systemic ChT	50.4 RBE/ 25 fx.	PB	mFT: 4.3 y 5-y: OS 45% DFS 25% 71% relapsed
Phan [62]	2016	60	SCC 40 pts. Non-SCC 20 pts.	Reirradiation 58% upfront surgery 73% ChT	66 RBE/30 fx	25% IMPT 75% PB	mFT: 13.6 m 1-y: LC 68.4% OS 83.8% PFS 60% DMFS 75% 30% toxicity G3.

Table 3.
Clinical experiences in head and neck cancer treated with synchrotron technology (2014–2019). (mFT: median follow up time).

hypofractionated intensity modulated proton therapy (IMPT) and combinations of hypofractionated proton therapy with immunotherapy [63].

For early-stage non-small cell lung cancer (NSCLC), the optimal clinical context for proton beam therapy (PBT) is challenging due to the increasing evidence demonstrating high rates of local control and good tolerance of stereotactic ablative body radiation (SABR). The potential advantage may be significant in treating larger tumors, multiple tumors, or central tumors. Most of the published studies are based on passive scattering PBT. Dosimetric benefits are likely to increase whith pencil beam scanning/intensity-modulated proton therapy (IMPT) [64]. A prospective longitudinal observational study of 82 patients with unresectable primary or recurrent NSCLC treated with 3-dimensional conformal radiation therapy (3DCRT), IMRT, or proton therapy included patient-reported symptom burden, assessed weekly for up to 12 weeks with the validated MD Anderson Symptom Inventory. Despite the fact that the proton group received significantly higher target radiation doses ($P < 0.001$), patients receiving proton therapy reported significantly less severe symptoms than did patients receiving IMRT or 3DCRT [63]. (**Table 4**).

3.5 Esophageal cancer

Radiation therapy (RT) has become an important component in the curative management of esophageal cancer (EC). Since most of the ECs seen in the Western hemisphere (i.e., Europe and the United States) are located in the mid- to distal-esophageal locations, heart and lungs invariably receive significant radiation doses. Proton beam therapy (PBT) provides the ability to further reduce normal tissue exposure because of its lack of exit dose, which is expected to provide clinically meaningful benefit for at least some EC patients [90].

Investigators at MD Anderson Cancer Center have reported a phase IIb randomized trial comparing PBT and IMRT for patients with EC (NCT01512589). The primary endpoints are progression-free survival and total toxicity burden, which is a composite endpoint including serious adverse events and postoperative complications. Among the 145 patients randomized, total toxicity burden was 2.3 times higher for photon IMRT and the postoperative complications (50% of patients were operated) was 7.6 times higher in photon IMRT cohort. The 3-year overall survival was similar in both groups (44%) [91]. Results from prospective clinical trials will greatly improve our knowledge regarding the role and benefits expected from proton therapy for EC. (**Table 5**).

3.6 Hepatocellular cancer

Proton beam therapy has the unique dosimetric performance, particularly valuable for the treatment of hepatocellular carcinoma (HCC). Clinical data is available in a limited number of patients, especially from Japan. In a systematic review from 1983 to June 2016 to identify clinical studies on charged particle therapy for HCC, a total of 13 cohorts from 11 papers. The reported actuarial local control rates ranged from 71 to 95% at 3 years, and the overall survival rates ranged from 25–42% at 5 years. Late severe radiation morbidities were uncommon, and a total of 18 patients with grade ≥ 3 late adverse events were reported among the 787 patients included in the analysis.

The American Society for Radiation Oncology (ASTRO) issued a Model Policy on PBT in 2014 and PBT for HCC is covered by medical insurance in the United States. The Japanese Clinical Study Group of Particle Therapy (JCPT), the Japanese Society for Radiation Oncology (JASTRO), the Japanese Radiation Oncology Study

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Lin [65]	2016	11	II-III NSCLC	4D versus 3D Robust Optimization	66 RBE/33 fx	PB	4D robust optimization improved dosimetry in comparable targets.
Welsh [66]	2013	260	Primary NSCLC	SBRT photon vs. SBRT proton dosimetric comparison	50 Gy/4 fx	PB	SBRT protons: Same coverage, significant reduction dose in chest wall and lung.
Matney [67]	2013	20	NSCLC IIB-III	Randomized IMRT vs. PSPT. 4D-3D dose variables	60–70 Gy/ 30–35 fx	PB	-Target coverage maintained up to 17 mm in both. −2/11 pts. less susceptible to respiratory motion PSPT
Nguyen [68]	2015	134	NSCLC II-III inoperable	Concurrent CT −21 stage II −113 stage III	60–70 Gy/30–35 fx	PB	−4.7 y follow-up -mOS stage II: 40 months Stage III: 30 months. OS, DFS, LC no difference by stage.
Niedzielski [69]	2017	134	NSCLC stage III.	IMRT(85 pts) vs. PSPT(49 pts) Esophageal toxicity (clinical and image)	60–70 Gy/30–35 fx	PB	No significant difference in esophageal toxicity found between proton and photon-based radiation therapy for the study cohort, based on imaging biomarker or CTCAE grade
Ohnishi [70]	2019	669	NSCLS stage I 38% T1a; 31% T1b; 29% T2a.	Efficacy and safety PBT	74–113 Gy	PB	3-y OS 79,5%. >100 GyE improved outcomes
Elhammali [71]	2019	51	Advanced inoperable NSCLC	Concurrent Cht	67.3 Gy	IMPT	3-y LC 78%. mOS 33 months,DFS 12 months. G3 toxicity 18%
Nakajima [72]	2018	55	Stage I NSCLC IA 33 pts. IB 22 pts	Image-guided fiducials (71%)	66 Gy/10fx 72 Gy/ 22 fx	PB	3-y OS 87%; 74% DFS; 96% LC No G3 toxicities.
Nantavithya [73]	2018	19	Inoperable stage NSCLC with HR features.	SBRT vs. SBPT	50 Gy/4 fx	PB	3-y OS 27% LC 90%

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
McAvoy [74]	2013	33	Recurrent after RT 63 Gy/33fx. III 20 pts.	Area of failure after initial RT: 19 pts. "in field". 31 pts. concurrent ChT.	63 Gy/33 fx	PB	1-y OS 47% DFS 28% LC 54% Toxicity≥3G pulmonary 21%
Gomez [75]	2013	25	NSCLC, thymic, carcinoid tumors.	Phase I. Dose-escalation hypofractionated PBT	45–52.5-60 Gy/15 fx.	PB	Dose-limiting toxicity: 2 pts. experienced fistula (52,5Gy). 60 Gy pneumonitis G4
Xiang [76]	2012	84	Stage III NSCLC	Concurrent Cht FDG uptake correlate (SUV1 pre, SUV2 post)	74 RBE/35 fx	PB	KPS and SUV2 were independently prognostic for LRFS, DMFS, PFS and OS.
Gomez [77]	2012	108	Stage III NSCLC (50–70% pts)	Esophagitis Concurrent ChT 405 3DCRT 139 IMRT 108 PBT	≥50 Gy/25–30 fx	PB	Esophagitis ≥ G3 -3DCRT 28% -IMRT 8% -PBT 6%
Koay [78]	2012	44	Stage III NSCLC	Concurrent ChT Analyze dosimetric variables and outcomes after adaptive replanning	74 RBE/37 fx	PB	-Adaptative planning more often performed in large tumors. −107.1 cm^3 adaptive VS 86.4 cm^3nonadaptive. - Median n° fx: 13 -Improvement in esophagus and SC.
Register [79]	2011	15	Stage I NSCLC	Central or superior tumors. Photon SBRT vs. PSPT vs. IMPT	50 Gy/4 fx	PB/IMPT	When the PTV was within 2 cm of the critical structures, the PSPT and IMPT plans significantly reduced the mean maximal dose to the aorta, brachial plexus, heart, pulmonary vessels, and spinal cord.
Chang [80]	2011	44	Stage III NSCLC	Phase II study Concurrent ChT	74 RBE/35 fx	PB	1-y OS 86%; PFS 63% Non-haematological G3 toxicity: 5 dermatitis, 5 esophagitis, 1 pneumonitis. n = 9 local recurrence.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Shusharina [81]	2018	83	Inoperable II-III stage. Oligo-mtx NSCLC	Compare lung injury IMRT vs. PBT revealed by ^{18}F-FDG post-treatment uptake	74 RBE/ 37fx	PB	The slope of linear 18F-FDG-uptake – dose response did not differ significantly between the two modalities
Jeter [82]	2018	15	Stage II-III NSCLC	Phase I study. Integrated simultaneous boost for dose-escalation IMRT (6) vs. IMPT (9).	72 Gy IMRT 78 RBE IMPT	IMPT	Grade ≥ 3 pneumonitis developed in 2 of the 6 patients treated to 78 Gy(CGE) IMPT SIB
Chang [83]	2017	64	Unresectable stage III NSCLC -IIIA 47% -IIIB 53%	Phase II study Concurrent ChT	74 RBE/37fx	PB	mOS 26 months 5y PFS 22%; LRR 28% Late pneumonitis G2 16% G3 12% 3% bronchial stricture.
Chang [84]	2017	35	Early stage (IA-II). 12 T1N0 23 T2–3 N0	Phase I-II prospective inoperable dose-escalated PBT	87 RBE/35fx	PB	-Median follow up: 83 months. −5-y OS 28% LC 54% Pneumonitis G2 11%; G3 3% Heart G2 5,7%; Chest wall 2,9%.
Chao [85]	2017	52	IIIA 51%. Recurrent NSCLC	Re-irradiation 67% concurrent ChT	66 Gy 30–74 RBE	PB	42% ≥ G3 toxicity. The 1-year rates of overall and progression-free survival were 59% and 58%, respectively.
Giaddui [86]	2016	52	Inoperable stage II-IIIB	Compliance criteria RTOG 1308: Phase III 26 IMRT vs. 26 PBT	70 RBE/35fx	PB	RTOG 1308 dosimetric compliance criteria are feasible and achievable
Wang [87]	2016	82	Locally advanced NSCLC.	3DCRT (22) vs. IMRT(34)vs. PBT(26) Patient-reported symptom burden	Higher radiation target dose used PBT	PB	Patients reported significantly less severe symptoms (pain, fatigue, lack of appetite, sleep and drowsiness).
McAvoy [88]	2014	99	Reirradiation for intrathoracic recurrent NSCLC	Concurrent ChT	60 EQD2 Reirradiation dose. 70 Gy median inital dose.	IMPT	Toxicity ≥ G3 7% esophageal and 10% pulmonary. Median LC,DMFS, and OS times were 11.43 months, 11.43 months, and 14.71, respectively.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Lopez Guerra [89]	2012	60	−80% stage III-IV. −40% squamous cell −35% adenocarcinoma	-Change in pulmonary function over time with PBT -Concurrent ChT. -PBT (60) vs. 3DCRT (93) vs. IMRT (97)	74 RBE	PB	Lung diffusing capacity for carbon monoxide is reduced in the majority of patients after radiotherapy with modern techniques. Multiple factors, including gross tumor volume, preradiation lung function, and dosimetric parameters, are associated with the DLCO decline.

Table 4.
Clinical experiences in lung cancer treated with synchrotron technology (2011–2019).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Ono [92]	2019	202	100 patients stage III/IV	90 inoperable patients.	87,2 median BED	4 PB centers	5y OS 56,3% 5Y LC 64,4%
Fang [93]	2017	448	IA-IVA III 56%	IMRT vs. PBT Lymphopenia	50.4 Gy/28 fx	PB	Significant less lymphopenia in lower esophagus
Xi [94]	2017	343	I-III III 65%	CRT definitive IMRT vs. PBT	≤50,4 Gy/28 fx 87%	Only 7 IMPT (5,3%)	PBT significant better OS,PFS,DMFS,LRFFS
Shiraishi [95]	2017	272	IIA-IVA III 59% 94% lower third 94% adenoca.	Neoadyuvant CRT IMRT vs. PBT lymphopenia	50,4 Gy/28 fx	PB	G4 lymphopenia 40% vs. 17% during nCRT
Prayongrat [96]	2017	19	IIB + III 80% 63% Distal third	CRT (4 surgery)	50,4 Gy/28 fx	IMPT single field 13	84% complete response. 4% surgery. G3 esophagitis (3 pts) 1-y OS 100% Mean heart dose 7.5 Gy
Shiraishi [97]	2017	727	I-IVA III 60% 89% Distal third	477 IMRT 250 PB DVH comparisons//Cardiac dose// Surgery 50%	50,4 Gy/28 fx	IMPT 13	Significant lower radiation exposure, MHD (chambers and coronary arteries).
Lin [98]	2017	580	I-IV III 63%	37% 3D 44% IMRT 19% PB Postop morbidity+outcome lenght in hospital. Stay LOS	50,4 Gy/28 fx	3 institutions (1/3 PB)	LOS: 3D 13.2d IMRT 11.6 d PB 9.3 d Pulmonary+cardiac+wound complications
Yu [99]	2016	11	100% Distal and GEJ	4D robust CT calculations	Dosimetric comparison	IMPT	Changes of water equivalent thickness ΔWET inspirations and espiration
Echeverria [100]	2012	100	I-IV III 51% 82% Distal third	Pneumonitis CTCAEv4 Re-staging PET-CT FDG 100%	50,4 Gy/28 fx	PB	Linear dose–response on FDG PET-CT. Symptomatic pts. had higher dose response slope.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Lin [101]	2012	62	I-IV II-III 84%	CRT + surgery (46%) Stage II + III (84%) Adenocarcinomas (76%)	50,4 Gy/28 fx	PB	Esophagitis 46% ypT0N0 28% 5y OS 37% Mean CR 50%
Zhang [102]	2008	15	I-IV	4DCT scan VS IMRT	50,4 Gy/28 fx	PB	3D vs. 4D plans % Gy sparing spinal cord MaxD. 2 fields vs. 3 fields: Better lung sparing, less conformality target.
Lin [103]	2020	145	II-III	Induction ChT IMRT vs. PBT randomized	50,4 Gy/28 fx	PB IMPT (20%)	Total toxicity burden and postoperative complications significantly lower in PBT cohort. 3-y OS 44%.

Table 5.
Clinical experiences in esophageal cancer treated with synchrotron technology (2012–2019).

Group (JROSG) and other groups are conducting multi-institutional prospective clinical trials in order to obtain approval for national health insurance for HCC and other cancers. The NCCN guidelines recommend that PBT may be appropriate in specific situations. In the Japanese guidelines, can be considered for HCCs that are difficult to treat with other local therapies, such as those with portal vein or inferior vena cava tumor thrombus and large lesions. The Korean Liver Cancer Study Group also mentioned the efficacy of PBT in their guidelines [104]. Guidelines from expert hepatologists evaluating the of data available for HCC patients will influence on the pattern of clinical practice considering the option of PBT as upfront therapy in the decision-making process (**Table 6**) [105].

3.7 Lymphoma

In adult lymphoma survivors, radiation treatment with increase excess of radiation dose to organs at risk (OARs) does increase the risk for side effects, especially late toxicities. Minimizing radiation to organs at risk (OARs) in adult patients with Hodgkin and non-Hodgkin lymphomas involving the mediastinum is the decisive factor to select the treatment modality.

Proton therapy reduces the unnecessary radiation to the OARs and reduces toxicities, especially the risks for cardiac morbidity and second cancers. In modern guidelines for adult lymphoma patients, the benefit from proton therapy and the advantages and disadvantages of proton treatment are considered. The dosimetric advantage of reducing the unnecessary dose to lung, breast, heart, spinal cord, vessels, vertebrae, thyroid and other structures in certain lymphoma involvements can be significant and highly desirable for patients that will be extreme long-term survivors at risk for severe chronic conditions and second malignancies (**Table 7**) [112].

3.8 Prostate

PBT for prostate cancer patients has been a continuously growing option due to its promising characteristics of high precision dose distribution in the target and a sharp distal fall-off. Considering the large number of proton beam facilities in Japan, the further increase of patients undergoing this treatment will be related to the policies of the Japanese National Health Insurance (NHI) together with the development of medical equipment and technology. A review conducted review to identify and discuss research studies of proton beam therapy for prostate cancer in Japan (up to June 2018) included 23 articles (14 observational, focused on the adverse effects), and 7 interventional on treatment planning, equipment parts, as well as target positioning. Favorable clinical results of PBT were consistent and future research should focus on longer follow-up clinical data. PBT is a suitable treatment option for localized prostate cancer [116].

At present, as particle beam therapy for prostate cancer is covered by the Japanese national health insurance system (since April 2018), and the number of facilities practicing particle beam therapy has increased recently, the number of prostate cancer patients treated with particle beam therapy in Japan is expected to increase drastically [117]. (**Table 8**).

3.9 Miscellaneous neoplasms and oncological clinical conditions

PBT has been explored in a variety of cancer sites, histological subtypes and disease stages, including localized breast cancer, seminoma, pancreatic cancer, oligo-recurrences and other cancer conditions. (**Table 9**).

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Takahashi [106]	2019	31	HCC recurrent after PBT. Child-Pugh class A (90%)	Angiography+TACE or TA in previous PB	77 RBE/35 fx 72 RBE/ 22 fx 66 RBE/ 10 fx	PB	Abnormal staining of the irradiated liver parenchyma was observed in 22 patients
Chadha [107]	2019	46	Unresectable HCC Child-Pugh class A-B 1–3 tumors.	22% multiple 28% vascular 57% recurrent	97 RBE/ 15 fx BED ≥90 GyE BED <90 GyE	PB	2-y LC 81% OS 62% 13% G3 toxicity
Hsieh [108]	2019	136	85%Posthepatectomy No RT Stage I-II: 49% Stage III: 39% BCLC-C 60%	RILD	66 RBE/10 fx 72 RBE/22 fx 67 RBE/15 fx	PB	Unirradiated tumor volumen/gross tumor volumen and Child-Pugh independently predicts RILD in patients with HCC undergoing PBT
Sanford [109]	2019	133	Unresectable HCC PB 37%. Child-Pugh class A 83% Child-Pugh class B-C 17%.	Protons vs. photons ablative	45 Gy/15fx 30 Gy/5–6 fx Liver GTV: 24 Gy/ 15 mean dose	PB	Improved 2y OS 59 vs. 28%. Decrease RILD Less liver descompensations
Hong [110]	2016	92	Unresectable or locally recurrent HCC or ICC 47 HCC 37 ICC	No prior RT 29% vascular thrombosis. 27.3% mutiple tumors	67.2 RBE / 15 fx	PB	2-y LC 94% OS 63%; 46%
Grassberger [111]	2018	43	22 HCC 21 ICC	Flow citometry lymphocite populations. CTLs NK prior/during/ after.	67.5 RBE / 15 fx	PB	• mOS 0.6 months for HCC and 14.5 months for ICC patients. • Longer OS significantly correlated with CTLs. • 42 months follow-up.

Table 6.
Clinical experiences in liver cancer treated with synchrotron technology (2016–2019); RILD: radiation induced liver disease; mOS: median overall survival.

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Ricardi [113]	2017	138	I-II 73% III-IV 27% Mediastinal involvement 96% Bulky 57%. No-relapse; No-refractory	Consolidation ChT	21 RBE pediatric 30.6 RBE adults	PB	3-y DFS 92% No G3 radiation toxicities
Rechner [114]	2017	22	Early-stage HL: Mediastinal	-Dosimetric comparisons. -IMRT vs. PBT -DIBH vs. free breathing.	30.6 RBE/17 fx	PB	DIBH with PBT significantly reduced life of year lost compared to IMRT in FB
Zeng [115]	2016	10	Early-stage HL: Mediastinal	Dosimetric comparison IMRT vs. 3DCRT vs. IMPT	30.6 RBE/17 fx	IMPT	IMPT significantly reduced lung and cardiac doses.

Table 7.
Clinical experiences in malignant lymphoma treated with synchrotron technology (2016–2017).

A special challenge for defining PBT health value are geriatric cancer patients. Aging and chronic comorbidity is a medical reality in the present and future of oncology practice. It is projected that 1 of 5 Americans will be aged ≥65 years in 2050 and that 60% of cancers will occur in this group. As PBT resources are limited, centers have designed decision-making systems for prioritization. Elderly cancer patients are as fragile as pediatric oncology patients in terms of "normal" tissues protection importance, their tissues are not that "normal" at all but link to comorbid and biological senescence. A small pilot survey of international academic radiation oncologists with particular experience in geriatric care recommended a preference for irradiation with PBT, due to the age condition and cancer stage. Although this finding may sound provocative, it shows that, while currently inclined toward pediatrics, many practitioners see strong indications in the elderly population.

The Eurocare showed that the age-standardized death rate for cancer was ≥12 times higher among elderly persons than among younger persons, in part, because treatments most commonly associated with cancer cure are less commonly given to elderly patients. The use of PBT will, through reducing morbidity, make the delivery of curative therapy more possible, merits a serious thought. Older patients are more likely to be admitted for cancer treatment as a result of an emergency or at an advanced stage. These factors may be associated with increased costs. The societal cost of delayed or inadequate treatment will require formal measurement against the cost of these advanced radiation technologies. PT should now be regarded as a relevant method to limit the short- and long-term toxicity of irradiation and reduce the need for costly supportive care.

While research protocols no longer exclude patients based solely on age, many currently do so because of these patients' comorbidities. It is time to consider the inclusion of comprehensively assessed elderly men and women in clinical trials of PBT. It is among these patients that some of the greatest benefits may yet be revealed. Until specific trials report their findings, a proactive guidance for the

Authors	Year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Deville [118]	2018	100	Risk organ-confined.	Post-prostatectomy. 34% ADT	70.2 RBE	86% IMPT	• Favorable GU-GI toxicity. • Acute max toxicity: G0 14%, G1 71%, G2 15%, G3 0%.
Pan [119]	2018	693	3465 IMRT 312 SBRT	Radical RT		PB	2y: • Erectile dysfunction 21 vs. 28% • Urinary toxicity 33 vs. 42% • Bowel toxicity 20 vs. 15%
Iwata [120]	2018	520	7 institutions. Organ confined.	21% ADT	63–66 RBE/ 22fx	PB	5y bRFS: LR 97% IR 91% HR 83% Toxicity ≥G2 GI-GU 4%
Nakajima [121]	2018	526	Urinary toxicity Organ confined	NR	74 RBE/ 37 fx 78 RBE/ 39 fx 60 RBE/ 20 fx	PB	No G3 toxicity. G2 hypofractionation 5,9%.
Takagi [122]	2018	1375	Long- term. Organ confined	56% ADT	74 RBE/37 fx	PB	Toxicities GU 2% GI 3% 5y bRFS: LR 99% IR 91% HR 86% VHR 66%
Rana [123]	2016	10	Dosimetric comparisons: IMP vs. IMRT	Rectum Bladder Femoral Head	79.2 RBE	IMPT	Better dosimetric results with IMPT
Pugh [124]	2013	226	Passive scattered VS IMPT	QoL Sexual function GU-GI toxicity	76 RBE/ 38 fx	22 PB 65 IMPT	No toxicity or QoL differences between PB and IMPT.

Table 8.
Clinical experiences in prostate cancer treated with synchrotron technology (2013–2018); GU: genitourologic; GI: gastrointestinal; QoL: Quality of life; ADT: androgen deprivation.

Authors	year	N° patients	Stage histology	Multidisciplinar	Dose/N° fractions	Proton technique	Observations
Guttmann [125]	2017	23	Reirradiation for recurrent and secondary soft tissue sarcoma	Reirradation. 1°: Acute toxicities.	68.4 RBE/ 30–35 fx.	PB 78%.	mFT 36 months mOS 44 m 3-y LF 41% Extremity-spared amputation 70%.
Hashimoto [126]	2016	10	Cervix Locally advanced (IIB/IIIA)	WPRT: 3DCRT vs. IMRT vs. PBT	50.4 RBE/ 25 fx	IMPT	IMPT spared the small intestine, colon, bilateral femoral heads, skin and pelvic bone to a greater extent than the other modalities.
Haque [127]	2015	1	Seminoma.Initial stage IA. Salvage radiation	IMRT vs. PBT	30 RBE/15 fx	PB	Complete response with no radiation-related side effects at the 3-month follow-up.
Pan [128]	2015	7	Mesothelioma IMRT n = 3 IMPT = 4	Pleurectomy n = 6	60RBE/ 25fx Integrated boost	IMPT	Dosimetric benefit shown in OARs. Lower mean doses to the contralateral lung, heart, esophagus, liver, and ipsilateral kidney, with increased contralateral lung sparing when mediastinal boost was required for nodal disease.
Demizu [129]	2017	96	Skull base n = 68 Cervical spine n = 8 Lumbar spine = 5 Sacral spine = 15	Surgery performed in 68 pts	<70Gy RBE (50pts) >70 Gy RBE (46pts)	PB	5-y OS 75% PFS 50% LC 71%
Smith [130]	2019	51	Reconstructed + — nodes	Post-mastectomy inmediate reconstruction	50 Gy/25 fx (73%) 40 Gy/15 fx (27%)	IMPT	Low rates of acute toxicity. More complications with hypofractionation. Max dermatitis G1 63%.
Mutter [131]	2016	12	I-III	Post-mastectomy inmediate reconstruction	50 Gy/25 fx (73%)	IMPT	Skin radiodermitis G3 in 1 patient.

Table 9.
Clinical experiences in miscellaneous neoplasms and cancer conditions treated with synchrotron technology (2015–2017); LC: Local Control.

allocation of geriatric patients to PBT in the non-study situation is needed urgently [132].

4. Clinica Universidad de Navarra Proton Unit: early clinical experience

In March 2020, after a 28 months installation period, the first cancer patient was treated. This is the first synchrotron equipment for PBT operating in Europe (**Figure 2**) and the third 360° gantry available for clinical use worldwide. (**Figure 3**). It is important to emphasize that the initiation of clinical activities was coincident with COVID pandemic, in one of the cities in the world (Madrid, Spain) with the more devastating epidemiologic and medical compromise. Under the strict institutional protective policy, none of the professionals involved in PBT intra-

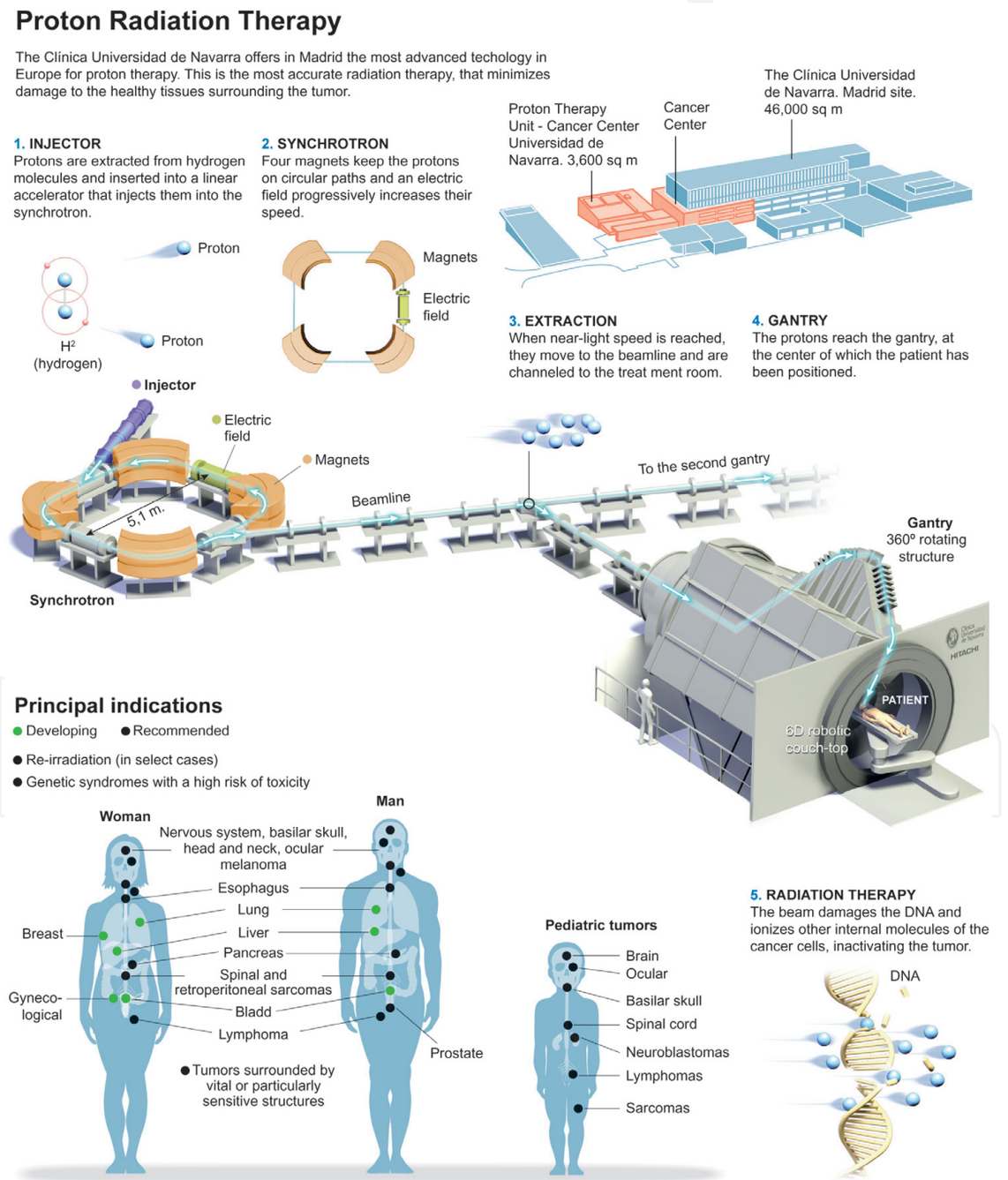

Figure 2.
Characteristics of the Proton Beam Therapy Unit structure at the Cancer Center Universidad de Navarra, CCUN (Madrid Campus, Spain).

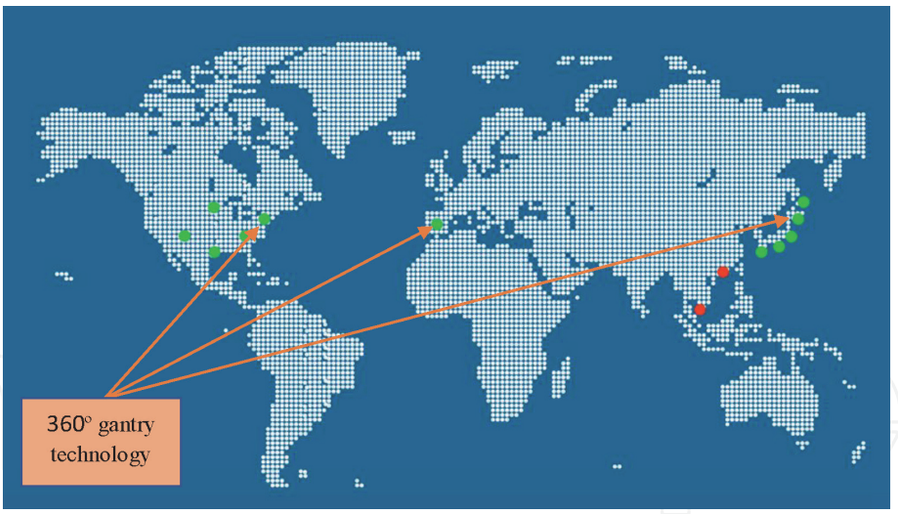

Figure 3.
Distribution of exclusive synchrotron technology for PBT in the world. Institutions with active 360° gantry equipment available.

hospital process have had a positive test for COVID infection (up to the moment of writing the present manuscript October 2020), but several patients (11%) under treatment were detected to be infected along the treatment period (**Table 10**).

Patient characteristics		
	#	%
N° patients		
	55	100
Age, years		
Median (range)	42 (3–86)	
<30	20	36.3%
>30	35	63.6%
Gender		
Female	29	52.7%
Male	26	47.3%
Reirradiation		
Yes	19	34.5%
No	36	65.4%
COVID-19		
Positive	6	11%
TUMOR		
Site		
Brain	17	30.9%
Skull base	4	7.3%
Head & Neck	7	12.7%
Thorax	5	9%
Spine	8	14.5%
Upper abdomen	2	3.6%

Patient characteristics		
	#	%
Pelvis	12	21.8%
Histology		
Chordoma/chondrosarcoma	9	16.3%
Rhabdomyosarcoma/Soft Tissue Sarcoma	3	5.4%
Medulloblastoma	5	9%
Ependimoma	3	5.4%
Craneopharingioma	2	3.6%
Malignant glioma	7	12.7%
Lymphoma	2	3.6%
Adenocarcinoma	11	20%
Squamous Cell	6	10.9%
Others	7	12.7%
TREATMENT		
Previous surgery Previous radiotherapy Concomitant ChT	33 19 10	60% 34.5% 18.1%
Proton Beam technique		
IMPT MFO synchrotron	55	100%
N° incidences (median, range)	3 (1–4)	
1 2 3 >3	1 15 27 12	1.8% 27.3% 49% 21.8%
Total doses		
<30 Gy RBE >30 Gy RBE	2 53	3.7% 96.3%
Fractionation (median, range)	24 (5–37)	
<10 10–20 >20	2 20 33	3.6% 36.3% 60%
Volume		
-Focal -Extended	32 23	58.2% 41.8%

Table 10.
Early clinical demographic data in patients treated in the Clinica Universidad de Navarra synchrotron PBT system: 6 months period (March–October 2020).

5. Conclusions

In principle, PBT offers a substantial clinical advantage over conventional photon therapy. This is because of the unique dose-deposition characteristics of protons, which can be exploited to achieve significant reductions in normal tissue doses proximal and distal to the target volume. These may allow escalation of tumor doses and greater sparing of normal tissues from unnecessary irradiation exposure, thus

potentially improving local control and survival while at the same time reducing toxicity, carcinogenesis and improving quality of life. Synchrotron technology matches these benefits with proven reproducibility of its dosimetric properties and clinical observations.

Despite the high potential of PBT, the clinical evidence supporting the broad use of protons is still under consolidation. The clinical data generated in institutions with synchrotron technology is abundant and of high scientific quality in terms of bibliometric records. An update has been summarized in the present publication. Clinical scientists operating with synchrotron proton beams are remarkably active in generating knowledge on topics such as cost effectiveness, the implementation of randomized trials and the collection of outcomes data in multi-institutional registries.

Some fundamental issues to understand clinical outcomes are unsolved. This includes the equivalence of passive beams versus pencil beam radiation delivery and the relative biological effectiveness (RBE) of protons which is simplistically assumed to have a constant value of 1.1. In reality, the RBE is variable and a complex function of the energy of protons, dose per fraction, tissue and cell type, end point, etc.

From 2012 to 2017, both ASTRO's Emerging Technology Committee report and ASTRO Model Policy document on proton beam therapy consider its recommendation reasonable in instances where sparing the surrounding normal tissue cannot be adequately achieved with photon-based radiotherapy and is of added clinical benefit to the patient. Based on the medical necessity requirements or the generation of clinical evidence in IRB-approved clinical trials or in multi-institutional patient registries adhering to Medicare requirements, PBT is expanding widely in clinical practice [133].

For a practicing oncologist evaluating treatment plans has uncertainties about the radiobiological equivalences (RBE) and other dosimetric elements that are taken into current models, which means that, the dose displayed on a commercial treatment plan is likely to be less accurate. These features are not intuitive for oncologists and allied cancer specialties clinicians and need further refinement in the assessment of dosimetric displays. It means the dose effects may extend past the isodose lines shown on paper, not considering certain uncertainties and this effect beyond the target will always be in non-target normal tissues [134].

Synchrotron technology is a component of the integral health care of a patient requiring radiotherapy and all the elements involved in the medical process need to be optimized to achieve an improved quality and safety standards in proton cancer therapy [135].

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Conflict of interest

The authors declare no conflict of interest.

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