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Controversy

Proton beams in cancer treatments: Clinical outcomes and dosimetric comparisons with photon therapy

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ABSTRACT

Purpose: To review current evidence of the role of proton therapy (PT) in other tumors than skull base, sinusal/parasinusal, spinal and pediatric tumors; to determine medico-economic aspects raised by PT.
Material and methods: A systematic review on Medline was performed with the following keywords: proton therapy, proton beam, protontherapy, cancer; publications with comparison between PT and photon-therapy were also selected.
Results: *In silico* studies have shown superiority (better dose delivery to the target and/or to organs at risk) of PT toward photon-therapy in most of thoracic and abdominal malignant tumors. Potential benefits of PT could be: reduction of toxicities (including radiation-induced cancer), increase of tumor control through a dose-escalation approach, hypofractionation. Cost of treatment is always cited as an issue which actually can be managed by a precise patient selection making PT a cost-effective procedure. Comparison plan with photon therapy may be useful to determine the dosimetric and clinical advantages of PT (Normal Tissue Complications Probability).
Conclusion: PT may be associated with a great advantage compared to the best photon-therapies in various types of cancers. Accumulation of clinical data is on-going and will challenge the *in silico* data analysis. Some indications are associated with strong superiority of PT and may be discussed as a new standard within prospective observational studies.

Introduction

Radiotherapy represents with surgery and chemotherapy an important component of a therapeutic tripod in cancer care. Historically, photons were used for radiation therapy soon after the discovery of X-rays (1895) and since the very beginning of the XXth century, irradiation has been proposed for the treatment of skin carcinomas [1]. Gradually, photon therapy has been considered as the standard of care for radiation treatments.

In 1929, at the University of California, Berkeley, Ernest O. Lawrence invented the cyclotron. He won the Nobel Prize in 1939 for the invention, its development, and the results he obtained. The first suggestion that energetic protons could be an effective treatment method was proposed by Robert R. Wilson [2]. The first treatments were performed with particle accelerators built for physics research, notably at the Berkeley Radiation Laboratory in 1954 and at Uppsala in Sweden in 1957. Since the first publication which reported proton therapy clinical outcomes after pituitary irradiation [3] and mainly during the last two decades, proton therapy literature increased significantly with the interest in this alternative to photon therapy.

Role of proton therapy in cancer treatments

To date, well-demonstrated indications of proton therapy (PT) are primary eye tumors, pediatric tumors, skull base tumors, chordomas, spinal and pelvic chondrosarcomas.

PT indications are justified by its ability to deliver very high-dose gradients close to serial organs while avoiding their maximum dose constraints. Tumors close to these serial organs are very likely to benefit from PT and are often already treated with this technique such as: nasopharyngeal carcinoma, meningioma and other intracranial benign tumors (close to neurological structures), salivary gland tumors, retroperitoneal liposarcomas close to the spine and bowels.

Parallel organs at risk could also benefit from PT as they are sensible to the mean dose. PT dose prescription could be increased due to a large decrease of the irradiated volumes of organ at risk.

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Table 1
Dosimetric comparison between proton and photon therapy and clinical results of proton therapy in cancer treatments.

	Dosimetric endpoint	Absolute dosimetric improvement*	Clinical results
Non Small Cell Lung Cancer	Lung V5	14.4–20–22% [6,8,9]	*n* = 35 pts [16]:
	Lung V20	3.2–6–6–7.6% [6,8,9,14]	median follow-up = 16.9 months
	Lung V30	3.2% [8]	1 year OS: 81.8%
	Mean Lung Dose	5–5% [8,14]	*n* = 19 pts [17]:
	Heart V40	4 Gy [14]	median follow-up = 15 months
	Mean Heart Dose	4.5–7 Gy [8,9]	6 specific death
	Esophagus V60	5% [14]	*n* = 134 pts [15]:
	Mean Esophagus Dose	15 Gy [9]	median follow-up = 4.7 years
	Bone Marrow V10	95 cc [9]	median OS = 30.4 months
	Bone Marrow V20	99 cc [9]	
Breast Cancer (with nodal irradiation)	Heart V5	16.8–31.5% [23]	n = 12 pts (chest wall) [24]:
	Heart V20	10.4–10.8% [23]	median follow-up = 6 months
	Homolateral Lung V5	8–21.1% [23]	No acute grade 3-4 skin toxicities
	Homolateral Lung V20	5.5–9.1% [23]	No early cardiac/lung toxicities
	Heart Mean Dose	1.6 Gy (no nodal irradiation)	*n* = 30 pts (breast) [27]:
	Total Lung Dose V5	[25]	median follow-up = 9.3 months
	Mean LAD Dose	7.3–9.6 Gy [26]	One grade 3 acute skin toxicities
		13–34% [26]	28.6% grade 2 esophagitis
	Mean Contralateral Breast Dose	4.8–17.9 Gy [26]	
		1.3 Gy to 6.6 Gy [26]	
Esophageal Cancer	Lung V5	12.7–25.5% – 35.6% –	*n* = 19 pts,70–80 Gy, PT Boost [32]
	Lung V20	26% – 14.7–26.7% [28–31]	median follow-up = 111.3 months
	Lung V30	0.9–6.8% – 5.8% –	5-years local control rate = 84.4%
	Mean Lung Dose	7% – 7–13.4% [28–31]	5-years OS = 42.8%
	Stomach V50	0.5–3.7% [28]	*n* = 40 pts,64–70 Gy [33]
	Mean Liver Dose	3.4–3.5 Gy – 5.1 Gy –	median follow-up = 24 months
	Heart V25	5.1 Gy – 3.6–8 Gy [28–31]	2-years CSS rate = 77%
	Heart V40	10.2 to 30.1% [28]	2-years LRFS rate = 66%
	Mean Heart Dose	14.5 to 16.7 Gy – 10 Gy [28,30]	*n* = 19 pts (photons) + 25 (PT) [31]
	Mean LAD Dose	20.4–22.6% [28]	median follow-up = 20–24 months
	Mean Total Body Dose	2% – 8% – 23.5–46.1% [29–31]	4 G3-5 in photon group (21%)
		14.9–15.9 Gy – 9.3 Gy [28,30]	0 G3-5 toxicities in PT group (0%)
		14.7–17.2 Gy [28]	
		3.3 Gy [29]	
Head and Neck Squamous Cell Carcinoma	Max Spinal Corde Dose	10.4–16.8 Gy [36,38]	*n* = 15,66–70 Gy, CT + PT [41]
	Max Brain Stem Dose	13.8–10.2 Gy [36,38]	median follow-up = 28 months
	Mean Ipsilateral Parotide Dose	4.8–6–17 Gy [35,37,38]	clinical complete response rate = 93.3%
	Mean Controlateral Parotide	10 Gy [35,37]	No anterior G2-5 anterior xerostomia
	Dose	7–13 Gy [35,37]	*n* = 50 pts with oropharyngeal tumors
	Mean Oral Cavity Dose	26 Gy [36]	66–70 Gy [42]
	Esophagus	6 Gy [38]	median follow-up = 25 months
	Mean Controlateral SG Dose	9.6–20 Gy [37,38]	94% alive with no disease at last folllow-up
	Larynx		One local and one neck failure
Nasopharyngeal tumors	Max Spinal Corde Dose	2.2–14.5–29.3 Gy [43–45]	*n* = 2 pediatric pts [46]
	Max Brain Stem Dose	15.4–14.6 Gy [43,45]	1 pt 59.4 Gy without chemotherapy
	Max Optic Chiasm Distal Dose	7.7–24.5 Gy [44,45]	no grade 2–5 toxicities
	Mean Controlateral Parotide	5.6 Gy [45]	1 pt 71.3 Gy with chemotherapy
	Dose	6.4 Gy [45]	grade 3 mucositis
	Mean Ipsilateral Parotide Dose	8.8 Gy [45]	no relapse 4 years after treatment
	Mean Esophagus Dose	8 Gy [44]	
	Mean Temporal Dose	15.5 Gy [44]	
	Mean Inner Ear Dose	18.4 Gy [44]	
	Mean Thyroid Dose	5.9 Gy [44]	
	Mean Oral Cavity Dose		
Pancreas Adenocarcinoma	Mean Liver Dose	25 Gy [49]	*n* = 22 pts [54]:
	V20 Stomach	12.1% [49]	median follow-up = 11 months
	V15 Stomach	43% [52]	50.4–59.4 Gy with concomitant 5FU
	V20 Small Bowel	13.2% [49]	no grade 3–5 toxicities
	V15 Small Bowel	52% [52]	
	V15 Duodenum	6% [52]	
	Mean Kidneys Dose	1.7 Gy [49]	
	V18 Right Kidney	23.2% [51]	
	Integral Dose to the body	32% [49]	
Cholangiocarcinoma/ Hepatocarcinoma	Mean Liver Dose	7.6 Gy [55]	*n* = 19 pts, HCC,72 Gy [63]
	Mean Right Kidney Dose	1.4 Gy [55]	with severe cirrhosis median follow-up = 17 months
	Mean Left Kidney Dose	4.5 Gy [55]	One local Failure
	Mean Heart Dose	4.2 Gy [55]	2-years OS and PFS rate = 42%
	Mean Stomach Dose	9.6 Gy [55]	No grade 3-5 toxicities
	Mean Duodenum Dose	5 Gy [55]	*n* = 93 pts, HCC, CHC,67.5 Gy [58]
			median follow-up = 13 months
			2-year local controle rate = 96%
			2-year OS and PFS: 48% and 38%

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