15th World Congress on **Advance Cancer Research**

PROTON THERAPY IS NOT THE FUTURE…… IT'S THE PRESENT……..

Dr. Rogelio A. Robaina Escobar
Independent Proton Therapy Consultant (Radiation Oncologist)
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SUMMARY:

- Introduction: Historical perspective and evolution
- Characteristics of equipment
- Commercial proton therapy system
- Scientific evidence
- Conclusions

2

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- **Introduction: Historical perspective and evolution**
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- Commercial proton therapy system
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HISTORICAL PERSPECTIVE AND EVOLUTION OF CHARGED PARTICLE BEAM THERAPY

- **1895:** German physicist **W.C. Roentgen** discovers X-rays, making detection of tumors in the body much easier and non-invasive. Roentgen later wins the Nobel Prize in Physics for this discovery.
- **1919:** British physicist **Ernest Rutherford** demonstrates the existence of protons (elementary particles found in atoms).





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HISTORICAL PERSPECTIVE AND EVOLUTION OF CHARGED PARTICLE BEAM THERAPY

- **1931:** American physicist **Ernest O. Lawrence** invents the cyclotron, a machine used in proton therapy, which accelerates charged particles to high energy levels. (Awarded the Nobel Prize in Physics in November 1939).
- **1937:** The first clinical use of X-ray radiation therapy is carried out for the treatment of a patient with leukemia at the University of California at Berkeley. Congress passes the National Cancer Institute Act that authorizes annual funding for cancer research in the United States.



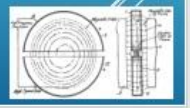


Diagram of the cyclotron in the 1934 patent

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HISTORICAL PERSPECTIVE AND EVOLUTION OF CHARGED PARTICLE BEAM THERAPY

- **1946:** American physicist **Robert Wilson** publishes a study that suggests protons could be used to treat cancer because they are capable of delivering an increased dose of radiation to a tumor while simultaneously decreasing radiation exposure to surrounding healthy tissue.
- **1948:** The first proton therapy experiments are conducted at the University of California at Berkeley. Tumors are effectively removed from the chest and lungs of animals.





Biological Use of Fast Protons

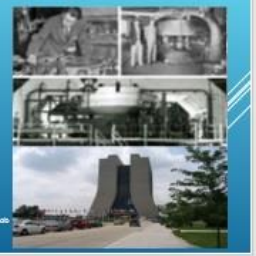
Published Online: Nov 1 1946

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HISTORICAL PERSPECTIVE AND EVOLUTION OF CHARGED PARTICLE BEAM THERAPY

- **1954:** The University of California at **Berkeley** treats the first human patient with protons. Patients are treated with proton therapy at other research institutions, including Harvard University in Boston.





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HISTORICAL PERSPECTIVE AND EVOLUTION OF CHARGED PARTICLE BEAM THERAPY

- **1990:** The world first hospital-based proton therapy facility was built in Loma Linda.
- **1996:** Developed spot scanning technique (PBS) in the PSI (Switzerland). First patient treated with spot scanning worldwide on November 25, 1996.
- **2008:** Dr. Andrew Lee, medical director of MD Anderson Cancer, was the 1st physician to treat patients with PBS in North America.
- **2013:** First compact system clinically used.



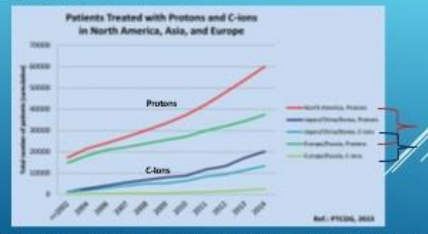
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Clinical advances
Technological advances
Biologic Advances



9

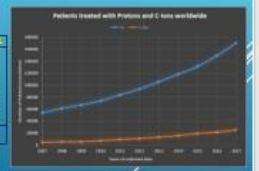
AS OF 2017, MORE THAN 199845 PEOPLE WORLDWIDE HAVE RECEIVED PROTON THERAPY AT CENTERS IN EUROPE, ASIA AND THE UNITED STATES



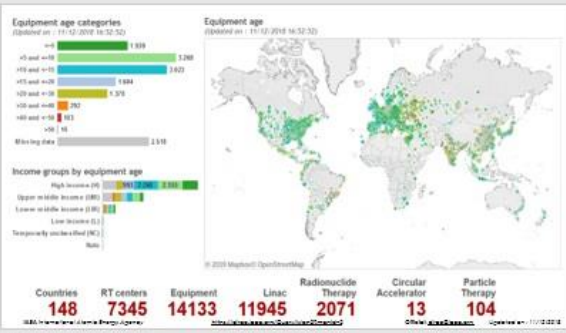
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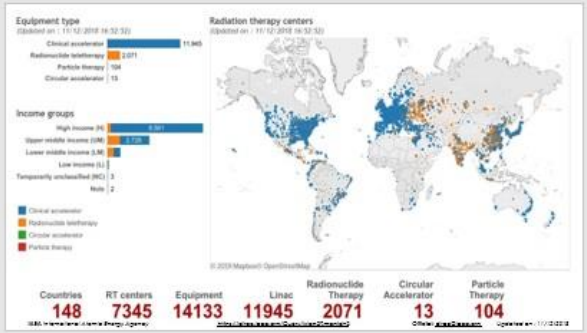
Summary 1954-2017	PARTICLES	PATIENTS TOTAL	DATES OF TOTAL
Total of all facilities (in and out of operation):	Hlc	2054	1957-1992
	Plans	1100	1974-1994
	C-ions	25703	1996-2017
	Other ions	433	1975-1992
	Protons	170256	1954-2017
	Grand Total	199845	1954-2017



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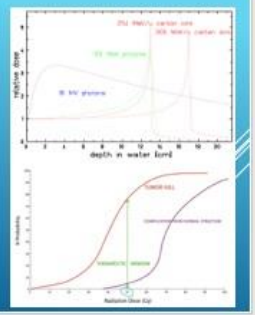
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13 ★

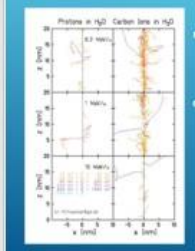
PROTONS: WHAT ARE THEY?

- A type of ionizing radiation, which due to their physical characteristics improve the deposit of doses in the tumor, protecting the adjacent healthy tissues.
- It allows to improve the therapeutic window.
- Efficacy demonstrated for years in the treatment of tumors in children.
- It is currently used in all locations, and is fundamentally useful in patients who require a 2nd irradiation, radio-resistant tumors.



14 ★

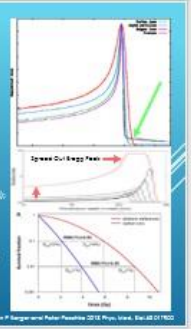
PROTONS vs CARBON-IONS



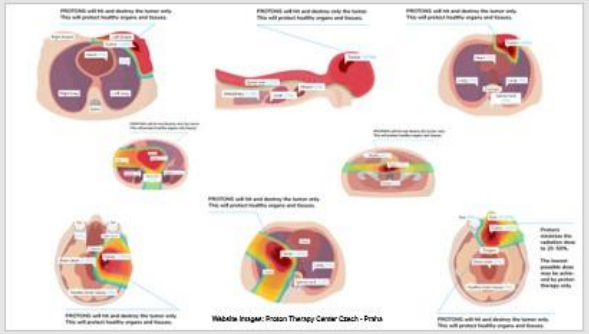
Protons:
- radiobiologically similar, (not photons);
- Better distribution of physical doses;
- ≥5-x10 more oxygenative than photons;

Carbon Ions:
- similar physical distribution;
- Greater radiobiological lethality (hypoxia);
- ≥5-x10 more oxygenative than protons.

High-LET radiation is less dependent on indirect damage, lower dependence on O_2.



15 ★



16 ★

SUMMARY:

- Introduction: Historical perspective and evolution
- **Characteristics of equipment**
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17 ★

TECHNICAL ASPECTS OF PROTON THERAPY

Accelerators:

CYCLOTRON — *Isochronous*, *Synchrocyclotron*

SYNCHROTRON



18 ★

CHARACTERISTICS OF CYCLOTRON

- Cyclotrons accelerate particles along an outward spiral path and are held in that path by a static electromagnetic field perpendicular to the spiral path.
- Charged particles get injected into the center of the cyclotron into a vacuum chamber between two hollow D-shaped metal electrodes (called "dees").
- The firing of the RF voltage is switched between dees, accelerating the particles and increasing the diameter of their circular path with every revolution, turning it into a spiral.
- Needs a degrader in the beam line.
- Synchrocyclotron is a special type of cyclotron, in which the frequency of the driving RF electric field is varied to compensate for relativistic effects as the particles' velocity begins to approach the speed of light.



19 ★

CHARACTERISTICS OF SYNCHROTRON

- Synchrotrons, send particles into a closed-loop path, increasing their speed with each revolution by varying the intensity of the magnetic field and the radiofrequency.
- One drawback of synchrotrons is they cannot accelerate protons for other particles from standstill, so they require an accelerator.
- An RF power generator supplies an electromagnetic field to the specially molded and shaped cavity that converts the EBF power into electromagnetic waves that become resonant and build up inside the cavity.
- When the charge particles enter the cavity, the force and direction of the resulting electromagnetic field accelerates them along the loop.
- Doesn't require a degrader to vary the intensity.



20 ★



21 ★

SYNCHROTRON vs CYCLOTRON

Synchrotron: Beam accelerated on a single path, magnetic field is ramped pulsed beam, multiple-stage.

- *Advantages:*
  - Naturally variable energy, and for any particle (carbon ions).
- *Disadvantages:*
  - Current limited if low energy injection.
  - Beam current stability & low noise is difficult on small synchrotrons.
  - Fast and accurate beam current control difficult to achieve.
  - More complex, larger surface.
  - Requires an injector (LINAC) to accelerate particles.

Cyclotron: Acceleration on a spiral path fixed magnetic field continuous or pulsed (SC).

- *Advantages:*
  - No practical current limitation.
  - Beam current stability & noise specifications currently achieved on small cyclotrons.
  - Fast and accurate beam current control over 1000/1 range easy to achieve.
  - Low complexity, strong, very compact, small surface.
- *Disadvantages:*
  - Variable energy requires external Energy Selection System.
  - Activation of components near the degrader.
  - Currently there are no for carbon ions.

22 ★

SYNCHROTRON vs CYCLOTRON

	SYNCHROTRON	CYCLOTRON
Energy flexibility	High (fast extract)	Fixed (need degrader)
Typical diameter	7 m	4 m
Power consumption	Low	High (except scc)
Typical Beam size	1 – 10 mm	10 mm
Typical energy spread	0,1 %	0,5 %
Beam intensity	Sufficient	High
Beam delivery efficiency	~ 95 %	~ 50 – 95 %
Complexity	Flexible	Simple
Weight	Light	Massive
Approximate cost	$ 50 - 100 Million	$ 20 – 25 Million
Other cost	Lower	Higher

23 ★

SYNCHROTRON COMBINED: PROTON AND C-ION

Synchrotron at CNAO — *Synchrotron at MedAustron*





24 ★

TECHNICAL ASPECTS OF PROTON THERAPY

Beam Delivery:

- Fixed beam room
- Rotating gantry room
  - Eccentric / Isocentric
  - 360º / 190º

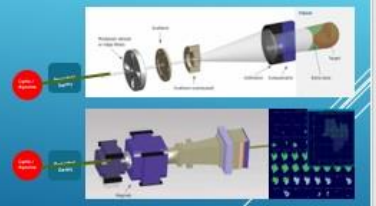


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TECHNICAL ASPECTS OF PROTON THERAPY

Beam Delivery:

- Passive Scattering (PS)
- Active Scanning
  Pencil Beam Scanning (PBS)



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PASSIVE SCATTERING (PS) (OLD SYSTEM)

- Single or double scattering.
- Cyclotron or Synchrotron is used to accelerate protons to therapeutic energies (typically 70 –250 MeV).
- Proton beam exists in a narrow mono-energetic state.
- Modulator: is used to bring the narrow mono-energetic proton beam to the desired energy.
- The energy specific beam now passes through one or two scattering devices. This expands the narrow beam into a wide beam.
- Multiple beams of various discrete energies are selected for treatment. The cumulative effect of treating with all of these beams is the creation of a Spread Out Bragg Peak.

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PASSIVE SCATTERING (PS) (OLD SYSTEM)



- **Collimator:** is placed between the wide mono-energetic beam and the patient. Usually made of thick brass. Used to shape the proton beam laterally.
- **Compensator:** is placed perpendicular to beam line in front of patient (generally but not always). Used to shape distal distally. Conforms maximum therapeutic dose to the distal edge of the tumor.

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PASSIVE SCATTERING (PS) (OLD SYSTEM)

Advantages

- Very sharp lateral penumbra due to use of apertures.
- Potentially more robust for motion mitigation. Some techniques deliver the entire SOBP at once.

Disadvantages

- Unable to conform dose to target proximally.
- Increased treatment time.
- Can be very arduous Forward planning. Time consuming.
- Not conducive to multitasking.

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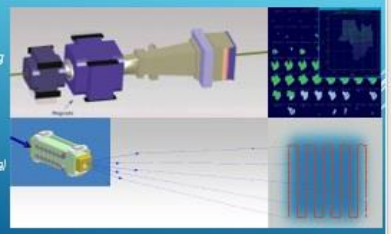
ACTIVE SCANNING PENCIL BEAM SCANNING (PBS)

- Cyclotron or Synchrotron is used to accelerate protons to therapeutic energies (typically 70 –250 MeV).
- Range (depth) dependent on the beam energy.
- Scanning magnets adjust the pencil beams position in both the X & Y direction.
- Different model of lateral scanning: discrete stop scanning (voxel to voxel), or line continuous scanning (intensity modulated scanning).
- The 3D volume is divided in several slices (LAYERS) perpendicular to the beams central axis. The dose in each layer is delivered by controlling simultaneously the pencil beam intensity and the location of the pencil beam SPOT in the X & Y direction.

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ACTIVE SCANNING PENCIL BEAM SCANNING (PBS)

- *Discrete stop scanning*
  (voxel to voxel)
- *Continuous scanning*
  (intensity modulated scanning)



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ACTIVE SCANNING PENCIL BEAM SCANNING (PBS)

Advantages

- Robust Optimization.
- Superior dose distribution as compared to passive scattering.
- Increased conformality.
- Increased uniformity in target coverage.
- Removal of manual junctions/feathering.
- Decrease of Beams.
- Decreased planning time in many complex cases.
- Faster turn around time from CT SIM to treatment. Decreased treatment time.
- All PBS proton therapy is technically IMPT.

Disadvantages

- QA can be more intensive and challenging.
- Increased lateral penumbra as compared to PS; (except hyperscan).
- This is likely to change in the future by planning PBS with apertures.

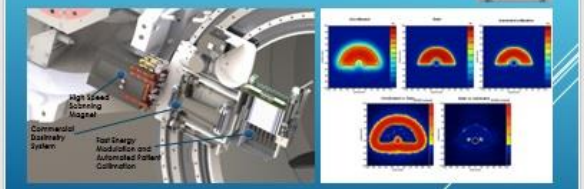
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HYPERSCAN (PENCIL BEAM OF MEVION) ADAPTIVE APERTURE IN PT(pMLC) 2017



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HYPERSCAN (PENCIL BEAM OF MEVION) ADAPTIVE APERTURE IN PT(pMLC) 2017



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COMMERCIAL PROTON THERAPY SYSTEM

Company	S/C/IC	Team
Mevion Medical Systems	SC	S250®
Ion Beam Applications (IBA)	C / SC	Proteus One®
Varian Medical Systems, Inc	C	ProBeam® Compact
Hitachi, Ltd.	S	PROBEAT™
ProNova Solutions, LLC	C	SC250®
Optivus Proton Therapy, Inc.	S	Conforma 300®
ProTom International	S	Radiance 330®
Mitsubishi Electric Corporation	S	
Sumitomo Corporation	C	
Siemens	S	
Toshiba	S	
LIGHT Proton System	Linac	



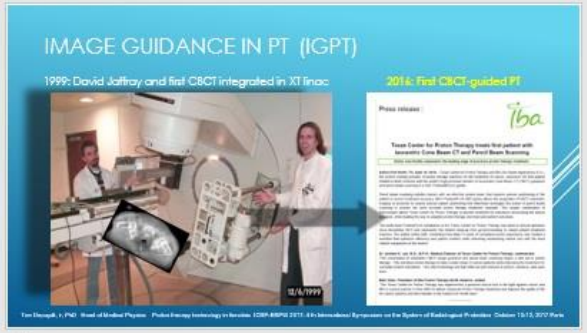
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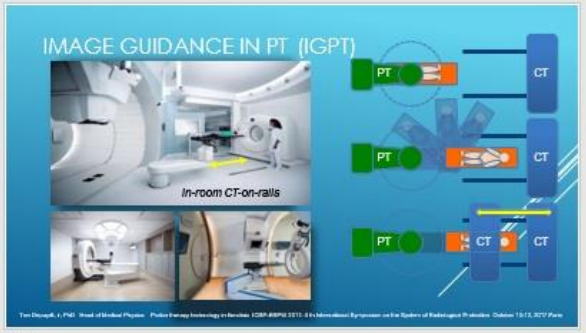
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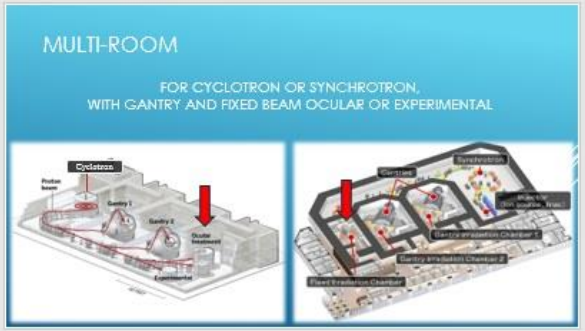
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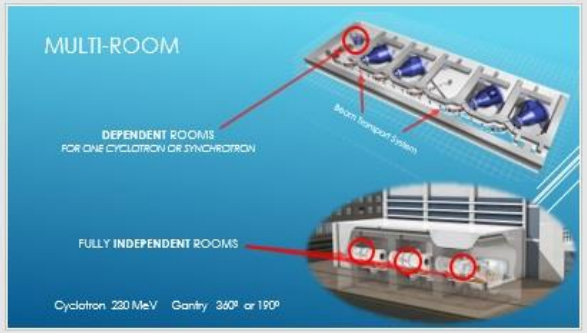
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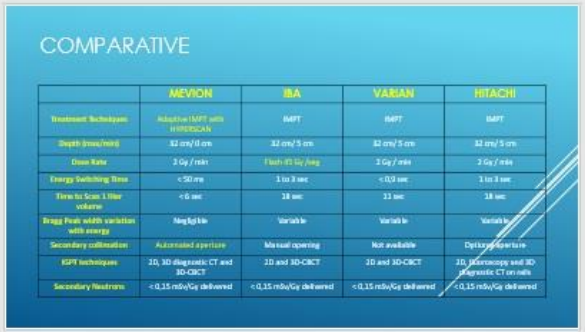
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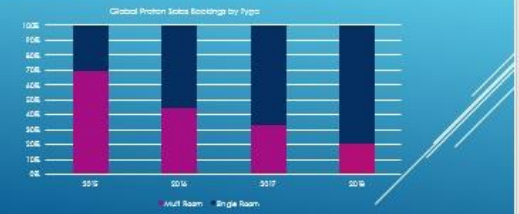
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MARKET TODAY:

Global adoption of compact single-room systems.

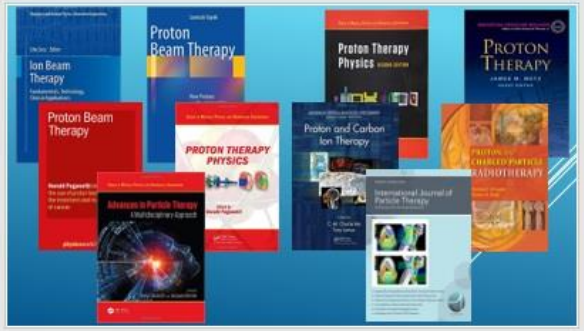


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WEB REFERENCES

- PTCOG (Particle Therapy Co-Operative Group): www.ptcog.ch
- NAPT (National Association for Proton Therapy): www.proton-therapy.org
- NCCN (National Comprehensive Cancer Network): http://www.nccn.org
- ASTRO (American Society for Radiation Oncology): https://www.astro.org/
- Proton Therapy Today: www.protontherapytoday.com
- PCG (Proton Collaborative Group): http://pcaresearch.org/
- Pediatric Proton Foundation: www.pediatricprotonfoundation.org
- Alliance for Proton Therapy Access : www.allianceforprotontherapy.org
- EPTN (European Particle Therapy Network by ESTRO): https://www.estro.org
- PubMed: www.ncbi.nlm.nih.gov/pubmed
- OncoLink: www.oncolink.org

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PROTONS: UTILITY

- Solid pediatric tumors.
- Chordomas and chondrosarcomas.
- Head and neck tumors.
- Tumors of the CNS.
- Uveal melanoma.
- Lung cancer.
- Lymphomas.
- Re - irradiations.
- Prostate cancer.
- Breast cancer.
- Esophageal cancer.
- Liver cancer.
- Pancreatic cancer.
- Anal and Rectal cancer.
- Gynecologic cancer.
- Soft tissue sarcoma.



Fondazione CNAO (Centro Nazionale di Adroterapia Oncologica) Pavia

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SOLID PEDIATRIC TUMORS



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CHORDOMAS AND CHONDROSARCOMAS



55

HEAD AND NECK TUMORS



56

TUMORS OF THE CNS



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UVEAL MELANOMA



58

LUNG CANCER



59

LYNPHOMAS



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RE-IRRADIATIONS


Evaluation of particle radiotherapy for the re-irradiation of recurrent intracranial meningioma

Proton beam reirradiation for locally recurrent pancreatic adenocarcinoma

Proton therapy for thoracic reirradiation of non-small cell lung cancer

HHS Public Access

Proton Beam Re-Irradiation for Recurrent Head and Neck Cancer: Multi-Institutional Report on Feasibility and Early Outcomes

61

PROSTATE CANCER


Early toxicity and patient reported quality of life in patients receiving proton therapy for localized prostate cancer: a single institutional review of prospectively recorded outcomes

Risk of subsequent primary cancers after carbon ion radiotherapy, photon radiotherapy, or surgery for localised prostate cancer: a propensity score-weighted, retrospective, cohort study

Five-Year Outcomes from 3 Prospective Trials of Image-Guided Proton Therapy for Prostate Cancer

Proton therapy vs. VMAT for prostate cancer: a treatment planning study

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BREAST CANCER

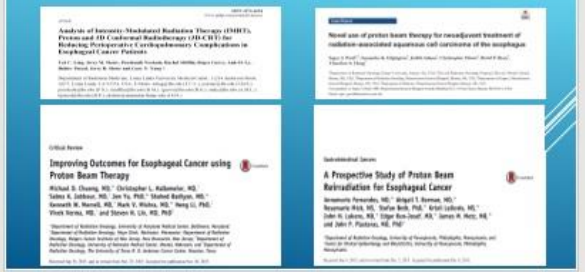

Improved long-term patient-reported health and well-being outcomes of early-stage breast cancer treated with partial breast proton therapy

Accelerated partial-breast irradiation using intensity-modulated proton radiotherapy: do uncertainties outweigh potential benefits?

Novel applications of proton therapy in breast carcinoma

63

ESOPHAGEAL CANCER


Analysis of Intensity-Modulated Radiation Therapy (IMRT), Proton and (4D Conformal Radiotherapy (4D-CRT) for Reducing Perioperative Cardiopulmonary Complications in Esophageal Cancer Patients

Novel use of proton beam therapy for neoadjuvant treatment of radiation-associated squamous cell carcinoma of the esophagus

Improving Outcomes for Esophageal Cancer using Proton Beam Therapy

A Prospective Study of Proton Beam Reirradiation for Esophageal Cancer

64

LIVER CANCER


A phase I trial of Proton stereotactic body radiation therapy for liver metastases

Long-term outcomes of proton beam therapy in patients with previously untreated hepatocellular carcinoma

Comparative study of the calculated risk of radiation-induced cancer after photon- and proton-beam-based radiosurgery of liver neoplasms

Patient-specific outcomes of charged particle therapy for hepatocellular carcinoma – A systematic review and quantitative analysis

65

PANCREATIC CANCER


Comparison of different treatment planning approaches for intensity-modulated proton therapy with simultaneous integrated boost for pancreatic cancer

Proton therapy for pancreatic cancer

Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes

Carbon Ion Radiation Therapy With Concurrent Gemcitabine for Patients With Locally Advanced Pancreatic Cancer

66

ANAL AND RECTAL CANCER


Accepted Manuscript

Dosimetric Comparison of Intensity-Modulated Proton Therapy and Volumetric-Modulated Arc Therapy in Anal Cancer Patients and the Ability to Spare Bone Marrow

67

GYNECOLOGIC CANCER


Initial Report of Pencil Beam Scanning Proton Therapy for Posthysterectomy Patients With Gynecologic Cancer

HHS Public Access

Bone Marrow Sparing in Intensity Modulated Proton Therapy for Cervical Cancer: Efficacy and Robustness under Range and Setup Uncertainties

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SOFT TISSUE SARCOMA


Salvage Carbon Ion Radiation Therapy for Locally Recurrent or Radiation-Induced Second Primary Sarcoma of the Head and Neck

Carbon ion radiotherapy for unresectable localized axial soft tissue sarcoma

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NCCN: NATIONAL COMPREHENSIVE CANCER NETWORK®


Central Nervous System Cancers

Uveal Melanoma

Prostate Cancer

Soft Tissue Sarcoma

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NCCN: NATIONAL COMPREHENSIVE CANCER NETWORK®


B-Cell Lymphomas

T-Cell Lymphomas

Thymomas and Thymic Carcinomas

Non-Small Cell Lung Cancer

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ASTRO UPDATES INSURANCE COVERAGE RECOMPENDATIONS FOR PBT


ARLINGTON, VA., JULY 10, 2017

Group 1 Indications, with additions marked by asterisks, include:

- Malignant and benign primary central nervous system (CNS) tumors*
- Advanced (e.g., T4) and/or unresectable head and neck cancers*
- Cancers of the paranasal sinuses and other accessory sinuses*
- Nonmetastatic retroperitoneal sarcomas*
- Reirradiation cases where cumulative critical structure dose would exceed tolerance dose*
- Hepatocellular cancer (no longer required to be treated in a hypofractionated regimen*)
- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of skull, including but not limited to chordoma and chondrosarcomas
- Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated
- Primary or benign axial tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when one of the criteria noted above apply
- Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients and retinoblastoma patients

Group 2 Indications if the patient is enrolled in either an institutional Research Board (IRB)-approved study or in a multi-institutional registry adhering to Medicare requirements for Coverage with Evidence Development (CED):

- Non-T4 and resectable head and neck cancers (previously all head and neck malignancies*)
- Nonmetastatic prostate cancer (previously grouped with genitourinary carcinomas*)
- Breast cancer*
- Thoracic malignancies, including nonmetastatic primary lung and esophageal cancers
- Abdominal malignancies, including nonmetastatic primary pancreatic, biliary and adrenal cancers
- Pelvic malignancies, including nonmetastatic rectal, prostate, bladder and cervical cancers

ASTRO

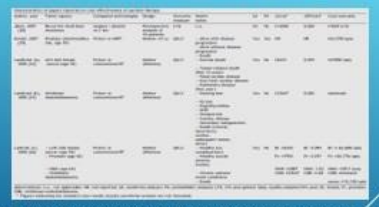
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SYSTEMATIC REVIEW: COST-EFFECTIVENESS

June 1st 2008



Conclusions: Evidence on the cost-effectiveness of PT is scarce. Adequate reimbursement is necessary to support such innovative yet costly treatments. For now, model-based economic evaluations performed at least from a health care perspective may help us to gain evidence-based insight into cost-effectiveness.

Cost of Proton Therapy — Cost-effectiveness of proton therapy: Current evidence and future needs — Radiotherapy and Oncology — Physics for clinicians

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SYSTEMATIC REVIEW: COST-EFFECTIVENESS

October 9, 2017



REVIEW

Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review

Vivek Verma, Charles B. Simone, II, Mark V. Mishra

Conclusions: Based on limited data, PBT provides favorable QOL/PRO profiles for adult brain, head/neck, lung, and pediatric cancers; measures for prostate and breast cancers were more modest. These results have implications for cost-effective cancer care and prudently designed QOL evaluation in ongoing trials, which are discussed. Future data could substantially change the conclusions of this review.

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PARACHUTE USE TO PREVENT DEATH AND MAJOR TRAUMA RELATED TO GRAVITATIONAL CHALLENGE: SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

- **What is already known about this topic.**
- Parachutes are widely used to prevent death and major injury after gravitational challenge.
- Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury.
- Studies of free fall do not show 100% mortality.
- **What this study adds.**
- No randomised controlled trials of parachute use have been undertaken.
- The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect.
- Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump.



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SUMMARY:

- Introduction: Historical perspective and evolution
- Characteristics of equipment
- Commercial proton therapy system
- Scientific evidence
- **Conclusions**

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CONCLUSIONS:

- Physical advantages:
  - Low dose to healthy tissues = low toxicity.
  - Low integral dose = low risk second neoplasms.
  - Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE) ↑ / = bigger benefits in radioresistant tumor.
- Scientific evidence supports the usefulness and benefit of proton therapy for patients with neoplastic diseases.
- More than 850 clinical studies show the benefit of the Proton Therapy. There are 104 particle therapy centers in the world, to December 2018.
- Efficiency, lower toxicity and cost effectiveness: they are not synonyms.

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CONCLUSIONS:

- The initial investment is high, but in the medium term compared to the high costs of chemotherapy and palliative treatments and with , it is clearly insignificant. More if it is seen as a treatment with curative intent.
- As professionals, we must disseminate and inform patients of these techniques already available in other countries, given that if we do not do this, we are hiding information.
- Politicians only see 4 or 5 years, but patients only think about their cure and continue living many more years.
- ***Responsibility, ethics, and work / Do not lie, do not steal, do not be idle (A. Mazal).***

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Proton Therapy is not the future.....
It's the present.....

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Thank you .....
on behalf of cancer patients

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