What's New in Radiation Therapy???

A Time to Heal Conference May 7, 2024

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A National Cancer Institute Designated Cancer Center



FRED & PAMELA BUFFETT CANCER CENTER

Disclosures

I have no conflicts of interest to disclose



Objectives:

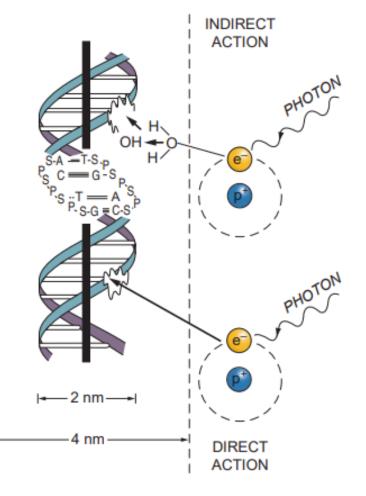
- Be able to describe how the combination of radiation therapy and drugs under development could spare normal tissue while increasing the cell killing effect of radiation therapy on cancer cells for anal cancer/rectal cancer
- 2. Be able to describe how combinations of radiation therapy and chemotherapy can be as effective as surgical removal of the bladder
- Be able to describe how stereotactic ablative radiation therapy can be used to treat renal cell carcinoma (kidney cancer) instead of surgery
- Describe the data that supports equivalence of prostate monobrachytherapy to combination external beam radiation therapy with a prostate brachytherapy boost
- 5. Describe the importance of combining androgen deprivation and radiation therapy for intermediate risk prostate cancer
- 6. Describe the development of clinical proton therapy in the USA
- 7. Describe what Flash Radiation Therapy is

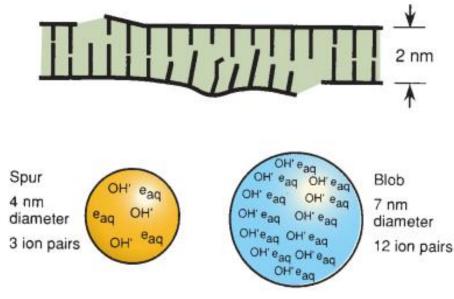


A Novel Drug Combined with Radiation Therapy

Radiation Biology 101 (aka Radbio)

Radiation Damages the DNA in the Cell







Radiation Biology 101 (aka Radbio)

Cells want to Survive including Cancer Cells

- Cancer cells with severe DNA damage Die! (Good)
- Cancer cell survivors see production of superoxide (O2•-) leading to growth of cancer cells by activating pro-survival factors (Bad)
- Superoxide (O2•-) inflammation in normal tissue and fibrosis (Bad)
- We need a way to Block Production of Superoxide (O2
 -) (Bad) & Protect Production of Hydroxyl Radical (OH
) (Good)



The Problem: Treatment of Anal Cancer with Chemo-Radiotherapy has Significant Side Effects

- Radiation Therapy (RT) & Chemotherapy CT) is treatment of choice for Locally Advanced Anal Cancer
- RT + 5-fluorouracil & mitomycin-C (CRT)
- Long-term disease-free survival and sphincter preservation
- RTOG trials showed 43-87% \geq grade 3 acute toxicity
- Grade 3: Severe or medically significant but not immediately life-threatening



The Overall Solution: Treatment of Anal Cancer with Chemo-Radiotherapy has Significant Side Effects

- Collaboration between oncology physicians and bench cancer researchers
- What if there was a drug in development that could protect normal tissue cells and simultaneously enhance killing of cancer cells



Fred & Pamela Buffett Cancer Center Facility Was Designed for Bench to Bedside Research



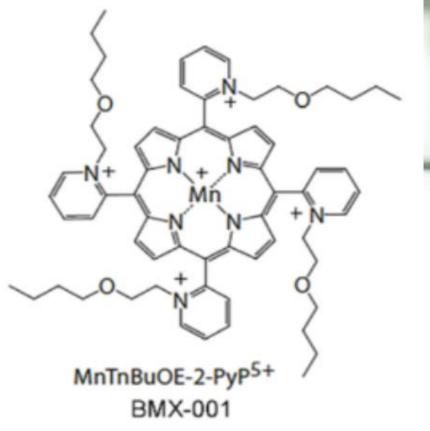
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BuffettCancerCenter.com Omaha, Nebraska

Introducing BMX-001 Developed by Rebecca Oberley-Deegan, PhD

MnTnBuOE-2-PyP (BMX-001) is a Superoxide Dismutase (SOD) mimetic & Potent Antioxidant (Good)

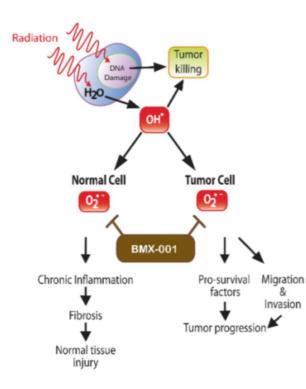






BMX-001 Protects Normal Cells but Not Cancer Cells

What is BMX-001?



- Radiation kills tumor cells by causing DNA damage by hydroxyl radical (OH•) production, which occurs in nanoseconds. Surviving irradiated tumor cells grow more aggressively.
- Metabolic production of superoxide (O2•-) drive growth of the tumors by activating pro-survival factors.BMX-001 inhibits O2•-, and thus, inhibits the ability of tumors to regrow after radiotherapy.
- BMX-001will not interfere with the initial tumor killing because it cannot scavenge OH•. O2•- can drive chronic inflammation in normal tissues, which ultimately lead to fibrosis.
- BMX-001 inhibits O2•- levels, which reduces chronic inflammation induced by cancer radiotherapy.



Combine BMX-001 with Standard CRT for Anal Cancer

PI: Chi Lin, MD, PhD, MS



- BMX-001 was given sub-cutaneous twice a week during CRT
- The maximum tolerated dose was not reached
- The recommended BMX-001 dose for a phase 2 trial was a loading dose of 28 mg and a twice weekly dose of 14 mg



1015 | VOLUME 111, ISSUE 3, SUPPLEMENT , S103, NOVEMBER 01, 2021

The Phase I Results of a Phase 1/2 Trial for Patients With Newly Diagnosed Anal Cancer Treated With Concurrent Radiation Therapy, 5-Fluorouracil, Mitomycin and BMX-001

C. Lin & J. Grem K. Klute ... A. Chatterjee E.A. Kosmacek R.E. Oberley-Deegan Show all authors

DOI: https://doi.org/10.1016/j.ijrobp.2021.07.239

	Grade 2+ Adverse Events			Grade 3 Adverse Events		
	RTOG 0529	RTOG 9811	BMX/ CRT	RTOG 0529	RTOG 9811	BMX/ CRT
Derm	39 (75%)	271 (83%)	8/11 (73%)	12 (23%)	159 (49%)	1/11 (9%)
GI	38 (73%)	237 (73%)	6/11 (54%)	11 (21%)	117 (36%)	0/11 (0%)
GU	8 (15%)	66 (20%)	1/11 (9%)	1 (2%)	11 (3%)	0/11 (0%)

MTD was never reached !!!



BMX-001 & Pre-operative CTX for Locally Advanced Rectal Cancer

- IRB: 012-22 received National Institute of Health R01 Grant Funding
- Patients with Stage II/III rectal cancer receiving pre-operative CTX & Surgery
- Patients receive pre-operative CTX with BMX-001
- Chi Lin, MD, PhD, MS is the Principal Investigator
- Dr. Deegan's drug, BMX-001, is the focus of the clinical trial



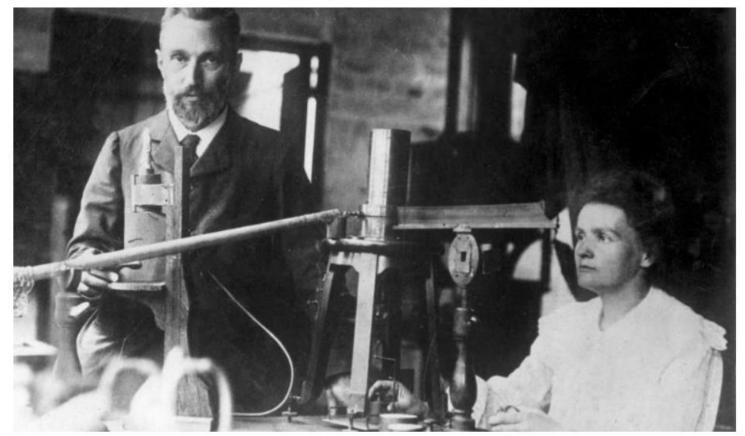
The Father of X-Rays November 8, 1895



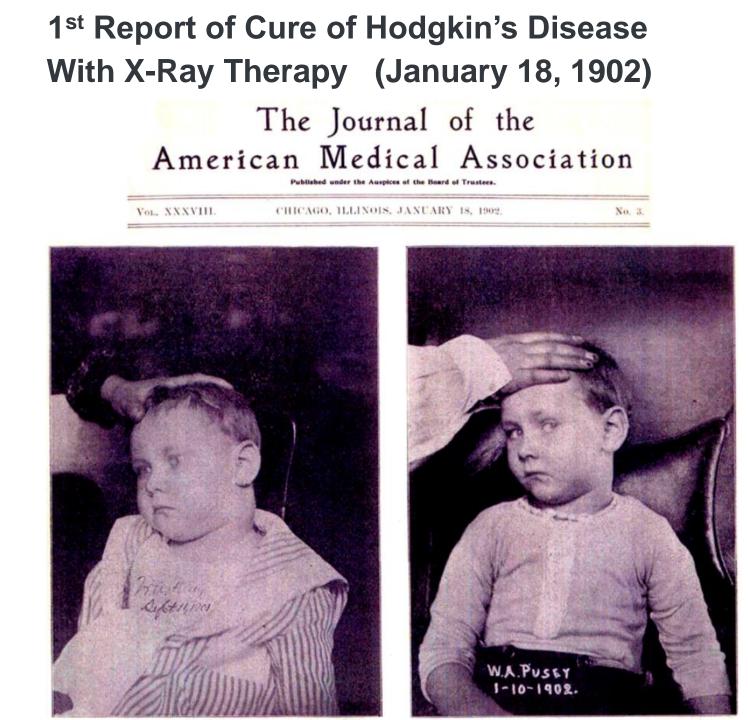
Röntgen in 1900



Discovery of Radium December 21, 1898 Marie and Pierre Curie







Self-Reflection

- Discovery of X-Rays to Present Time is 130 years
- I have been in practice for 35 years
- That is 26% of elapsed time dating to the discovery of X-Rays in the late 1800's!
- I have been a Department Chair at UNMC for over 26 years
- That is almost 20% of elapsed time since the discovery of X-Rays
- Can you say "Time Flies!"





What's New in Genitourinary Radiation Therapy???





Bladder Cancer-Bladder Preservation

Background:

- Radical cystectomy (surgical removal of the bladder) has long been considered the best treatment for bladder cancer
- Using radiation combined with chemotherapy was reserved for those unable or unwilling to have their bladder removed
- There has not been a clinical trial directly comparing these two treatment options



Bladder Cancer-Bladder Preservation

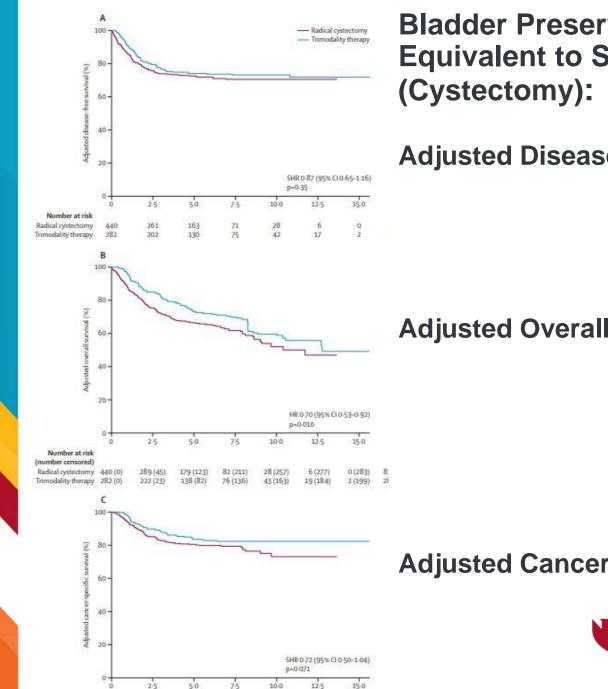
The Study:

- Alexandre R Zlotta, Leslie K Ballas, Andrzej Niemierko, Katherine Lajkosz, et al. Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis. The Lancet Oncology, Volume 24, Issue 6, 2023, Pages 669-681
- All patients were healthy enough to receive a radical cystectomy, but approximately ¼ received chemoradiation
- No difference in disease-free survival, development of metastatic disease, cancer-specific survival, or overall survival regardless of how patients were treated

Conclusions:

 Bladder preservation is now considered an equal option, allowing more patients to avoid an extensive surgery and keep their anatomy intact





Bladder Preservation with TMT is **Equivalent to Surgical Removal**

Adjusted Disease-Free Survival

Adjusted Overall Survival

Adjusted Cancer Specific Survival



Stereotactic Ablative Body Radiotherapy (SABR/SBRT) for

Renal Cell Carcinoma aka Kidney Cancer

Background:

- Ablative radiation techniques have become increasingly considered in the treatment of newly diagnosed renal cell carcinoma
- To date, all data for this has been retrospective; limiting widespread acceptance



Stereotactic Ablative Body Radiotherapy (SABR/SBRT) for Bonal Call Carainama aka Kidnay Canaar

Renal Cell Carcinoma aka Kidney Cancer

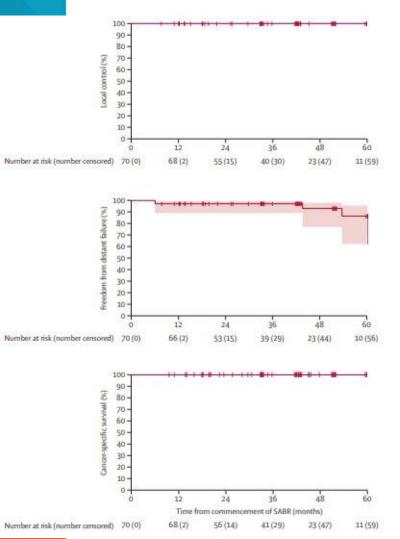
- The Study:
- Siva S, Bressel M, Sidhom M, Sridharan S, et al. FASTRACK II Investigator Group. Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial. Lancet Oncol. 2024 Mar;25(3):308-316.
- First prospective clinical trial of SBRT in RCC (1-3 fractions)
- **100% local control** through 5 years
- Only 3% developed distant metastatic disease at 3 years
- 36% toxicity rate with only 10% requiring medical intervention and none considered life-threatening

Conclusions:

• Short course ablative radiation is a good option for patients with newly diagnosed RCC and is becoming more widely accepted



Stereotactic Ablative Body Radiotherapy (SABR/SBRT) for Renal Cell Carcinoma aka Kidney Cancer



Local Control (%)

Freedom from Distant Failure (%)

Cancer Specific Survival (%)



Brachytherapy Monotherapy vs Brachytherapy + EBRT in Intermediate Risk Prostate Cancer

Background:

- For most patients with intermediate-risk prostate cancer, radiation treatment has classically required an external beam component consisting of many trips into clinic for treatment
- Prior clinical trials have suggested that a combination of external radiation (EBRT) in addition to internal radiation (brachytherapy boost) is the most effective treatment for prostate cancer



Brachytherapy Alone (Monotherapy) for Intermediate Risk Prostate Cancer

The Study:

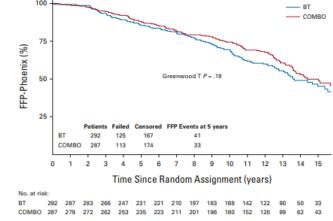
Michalski JM, Winter KA, Prestidge BR, Sanda MG, et al. Effect of Brachytherapy With External Beam Radiation Therapy Versus Brachytherapy Alone for Intermediate-Risk Prostate Cancer: NRG Oncology RTOG 0232 Randomized Clinical Trial. J Clin Oncol. 2023 Aug 20;41(24):4035-4044.

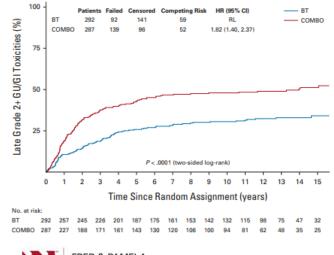
Compared EBRT (25 fractions)+ brachytherapy boost vs brachytherapy alone

No difference in cancer recurrence rates at 5 years post-treatment No difference in acute toxicities between the arms Patients treated with brachytherapy alone had a lower rate of long-term side effects

Conclusions:

Brachytherapy alone without EBRT is a viable and favorable treatment options for patients with intermediate-risk prostate cancer







Importance of Androgen Deprivation for Intermediate Risk Prostate Cancer

Background:

- Androgen deprivation therapy is well-established to improve outcomes in patients receiving radiation treatment for higher-risk prostate cancer
 - Much of this data came from an era when lower doses of radiation were used with hints that it in less important when using doses of radiation in line with modern treatment
- Past data has suggested that it may not be needed in patients with favorable intermediate risk or lower disease



Importance of Androgen Deprivation for Intermediate Risk Prostate Cancer

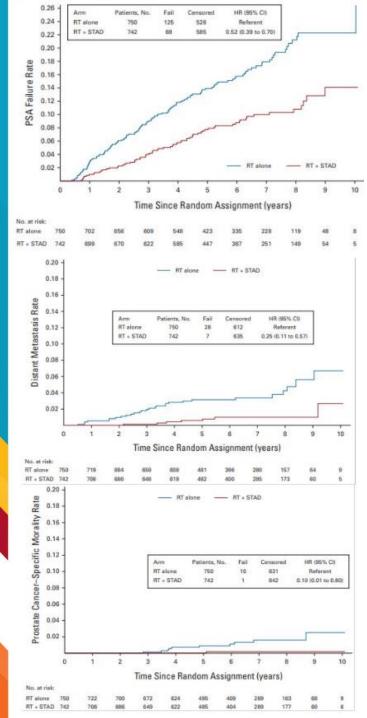
The Study:

- Krauss DJ, Karrison T, Martinez AA, Morton G, et al. Dose-Escalated Radiotherapy Alone or in Combination With Short-Term Androgen Deprivation for Intermediate-Risk Prostate Cancer: Results of a Phase III Multi-Institutional Trial. J Clin Oncol. 2023 Jun 10;41(17):3203-3216.
- Standard radiation (modern dose) +/- 6 months of ADT in patients with intermediate risk prostate cancer
- The addition of ADT cut the rate of cancer recurrence in half, reduced the risk of metastatic disease by 75% and reduced the risk of cancer-specific mortality by 90%

Conclusions:

 The addition of ADT improves patient outcomes all patients with intermediate risk prostate cancer, even when using high (modern) doses of radiation





Importance of Androgen Deprivation in Intermediate Risk Prostate Cancer

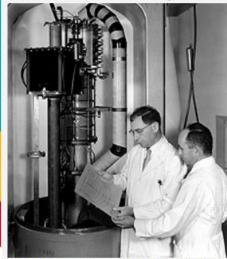
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Stanford University Develops 1st Linear Accelerator January 1956

Edward Gintzon, PhD and Henry Kaplan, MD

Department of Radiation Oncology



Henry Kaplan, left, and physicist Mitchell Weissbluth, at the working end of the Stanford accelerator.

Department of Radiation Oncology



The first patient to receive radiation therapy from the medical linear accelerator at Stanford was a 2-year-old boy.

Department of Radiation Oncology



The original linear accelerator in operation.

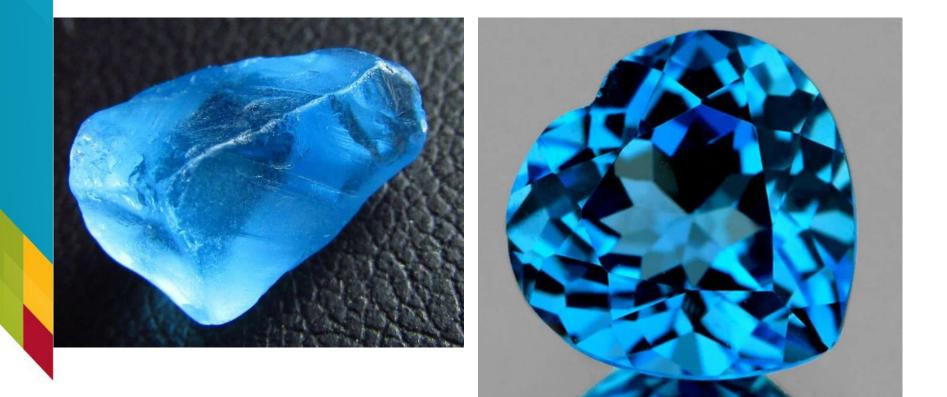


Take 1 Topaz and Expose it to Neutron Radiation and ...





...You get Blue Topaz (I promise, they are not radioactive)





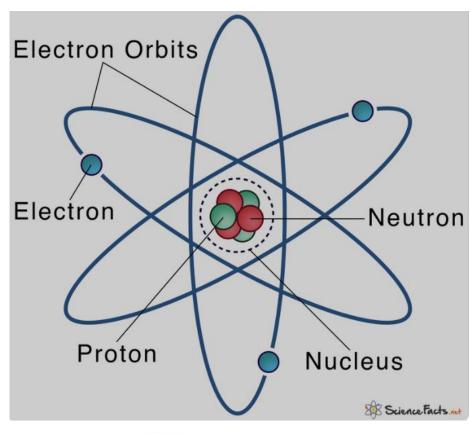
Proton Therapy

• 1929 Ernest Lawrence

Conceives of a cyclotron to accelerate particles like protons

- 1946 Robert R. Wilson
 Proposes the medical application of proton beams
- 1954 Berkeley Radiation Lab.
 1st human application of PT
- 1961 1st PT facility at Harvard
- 1988 FDA Approves PT
- 1990 Loma Linda UMC is 1st facility to offer PT exclusively for Cancer Treatment
- 1999 U of Pennsylvania opens its 1st of 3 PT facilities
- 2001 MGH opens PT facility featuring Pencil Beam Scanning
- 2012-2016 Number of USA PT Centers doubles. 70% increase in patients receiving PT
- 2024 45 Active Proton Centers in the USA

Lithium





Proton Therapy in the USA 45 operating centers – 6 in development





WHAT IS PROTON THERAPY? How it compares to conventional photon therapy



PROTON BEAM THERAPY: Delivers targeted doses of radiation directly to the tumor, greatly

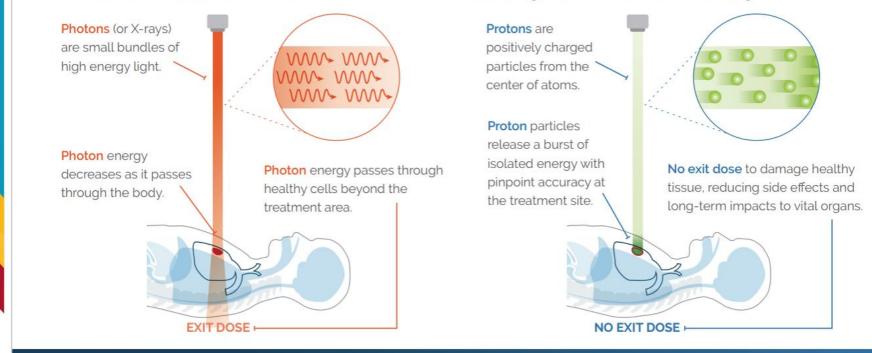
reducing the risk of serious and debilitating side effects.

The National Association for Proton Therapy

Proton therapy is a life-saving cancer treatment that delivers hope to patients around the world. **Backed by decades of science and delivered by proven technology**, proton therapy is ultra-precise, effective, and one of the most advanced cancer treatments available today.

CONVENTIONAL PHOTON RADIATION:

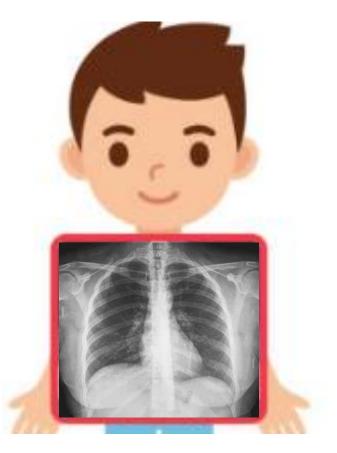
Delivers radiation to the tumor as it passes through healthy tissue on either side of the treatment site.





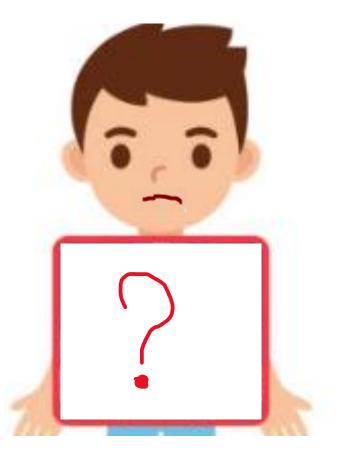
X-Rays are Absorbed Differently by Tissues Based on Their Density and Pass Through the Body to Expose Real or Digital Film to Make an Image



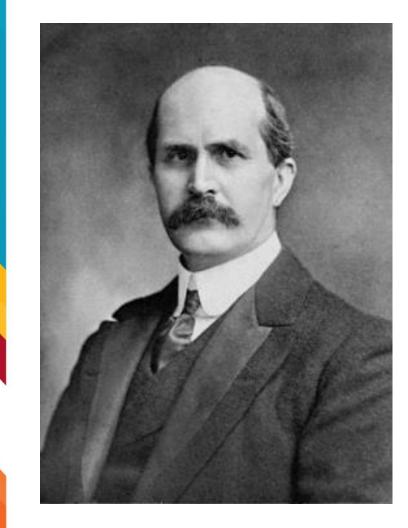


Proton Beams are Absorbed by Tissue in the Body and don't Exit the Body. Proton Beams can't be used to make Images





Sir William Henry Bragg 1862-1942



Bragg Curve

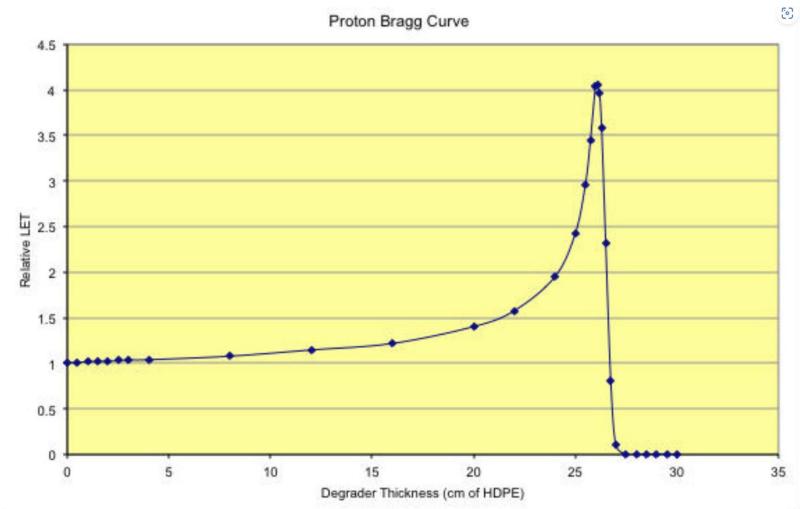
Plots energy loss of ionizing radiation therapy as it travels through matter

Bragg Peak

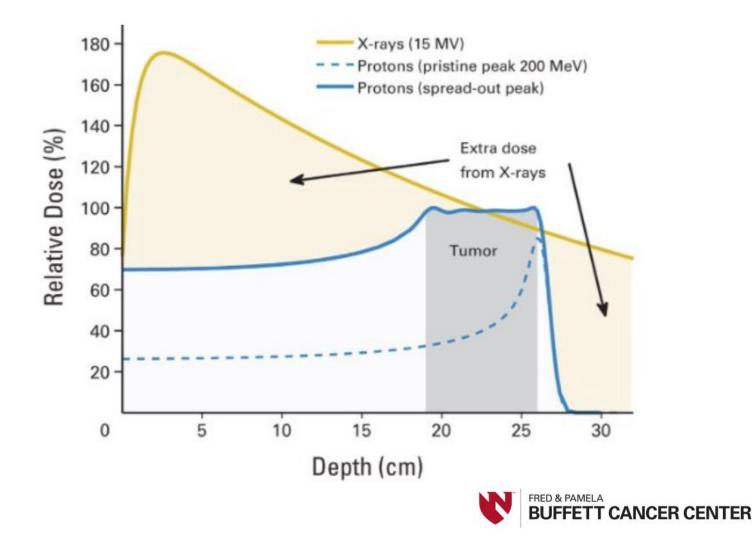
For protons, alpha-rays, and other ion rays, the peak in energy deposit in a substance immediately before the particle comes to rest



Proton Bragg Peak (Sir William Henry Bragg 1904)



Modified Proton Bragg Peak (Spread out Bragg Peak for Rx)



Medical Indications for Proton Therapy

- 1. Target is near an OAR needing sharp dose decrease
- 2. Proton Rx would decrease risk of serious side effects
- 3. The same/adjacent area has been previously treated



General Indications for Proton Therapy

BRAIN, SPINE & OTHER CENTRAL NERVOUS SYSTEM CANCERS

When treating brain and other central nervous system cancers, it is important to limit radiation doses to other critical structures such as the brain stem, spinal cord, and healthy brain tissue that control important body functions. Proton therapy is the most advanced radiation treatment technology available that can limit unnecessary radiation to these structures.

BREAST CANCER

Because the breast is located in close proximity to the heart and lungs, proton therapy holds distinct advantages over standard radiation therapy due to the ability to limit the radiation dose to the breast tissue. Standard radiation therapy deposits radiation into both the heart and lung increasing the chance for short and long term side effects including secondary cancers later in life.

ESOPHAGEAL CANCER

The esophagus is located adjacent to many critical organs and structures including the heart, lungs, trachea, and major blood vessels. Protection of these organs and structures is important in order to prevent significant side effects such as heart disease and radiation pneumonitis. Due to its precision and clinical advantages, proton therapy is ideally suited to reduce the risk of these side effects while delivering a curative dose to the tumor.

GYNECOLOGIC CANCER

Proton therapy may be a more precise radiation option for treatment of gynecologic cancers to help protect the function of important nearby organs like the bowels, bladder, and genitals, as well as reducing the risk of developing a future cancer.

HEAD & NECK CANCERS

Many critical structures are located in the head and neck area including the brain stem, spinal cord, and salivary glands. When treating in this area with high doses of radiation, significant side effects can occur including the inability to speak, swallow, and the loss of saliva production. Proton therapy can help reduce the risk of experiencing these side effects by limiting radiation dose to these structures.

LIVER CANCERS

The liver serves the critical function of filtering the bloodstream which often results in cancers originating in other areas of the body spreading to this critical organ. In addition, hepatocellular and intrahepatic cholangiocarcinoma (bile duct cancer) can originate in the liver. Recent studies have demonstrated that proton therapy patient's overall survival rates are higher than standard radiation therapy patients when treating these indications.



General Indications for Proton Therapy

LUNG CANCER

Like other cancers that occur in the chest area, there are many critical structures and organs that lie close to the lungs including adjacent healthy lung tissue. Because of the clinical advantages of proton therapy, radiation doses to critical organs such as the heart and healthy lung tissue can be limited resulting in decreased lung complications such as radiation pneumonitis and heart disease.

LYMPHOMAS

Lymphomas can occur in many different areas of the body often adjacent to critical structures and organs including the heart, lungs, kidneys, spinal cord, esophagus, bone marrow, stomach, and salivary glands. For this reason, proton therapy is advantageous by limiting the amount of radiation that is delivered to these critical structures and organs while delivering a curative dose to achieve tumor control.

OCULAR CANCERS & OTHER EYE CONDITIONS

Due to the unique physical characteristics of proton beams, proton therapy is clinically advantageous compared to standard radiation therapy when treating ocular cancers. Because of the location of the eye in relation to the optic nerve and surrounding brain tissue, proton therapy can limit harmful radiation doses to these critical structures and organs.

PEDIATRIC CANCERS

Pediatric cancer survival rates have increased significantly over the last decades from 10% to nearly 90% today. Proton therapy can limit radiation doses to healthy, developing tissues while delivering curative doses to the tumor which reduces pediatric cancer patients' risk of experiencing long-term side effects.

PANCREATIC CANCER

The pancreas is located in the mid-abdominal area surrounded by several critical organs including the liver, kidneys, stomach, and the small and large intestines. Due to this critical location and the radiation sensitivities of these organs, it is imperative to keep radiation doses to these organs limited to prevent nausea, vomiting and to preserve organ function. For these reasons, proton therapy is highly indicated to deliver a curative dose to the tumor and limit dose to these surrounding organs.

PROSTATE CANCER

The prostate is a walnut-shaped organ surrounded by the bladder and rectum that sits deep in the male pelvis. For this reason, these organs as well as the adjacent intestines and bony structures often receive unnecessary doses of radiation when treating the prostate for cancer. This can result in increased side effects both short and long term. Proton therapy can limit unnecessary radiation doses to these tissues when treating the prostate reducing debilitating side effects such as rectal urgency and frequency. Additionally, some studies have demonstrated increased survival rates for proton therapy patients when compared to patients treated with standard radiation therapy.

SARCOMAS

Sarcomas can occur in bone and soft tissue in many different areas of the body. These types of tumors require high radiation doses to achieve a cure. For this reason, when they occur adjacent to critical structures and organs, proton therapy is advantageous because it can limit the amount of unnecessary radiation resulting in fewer and less severe short and long term side effects.

SKULL-BASED CANCERS

Cancers that occur in the skull base are difficult to treat due to the close proximity of the brain stem, spinal cord and healthy brain tissue. Proton therapy has proven to be beneficial in delivering a curative dose to these tumors while limiting radiation to these critical structures and organs resulting in reduced short and long term side effects in these areas.



Pediatric Proton Therapy

- >80% of kids with cancer survive 5+ years
- Many can have a normal life expectancy
- The ideal radiation therapy limits dose to normal tissue
- Reduce risk of adverse impacts on: IQ/intelligence, cardiac, pulmonary, skeletal development
- Reduce risk of secondary cancers



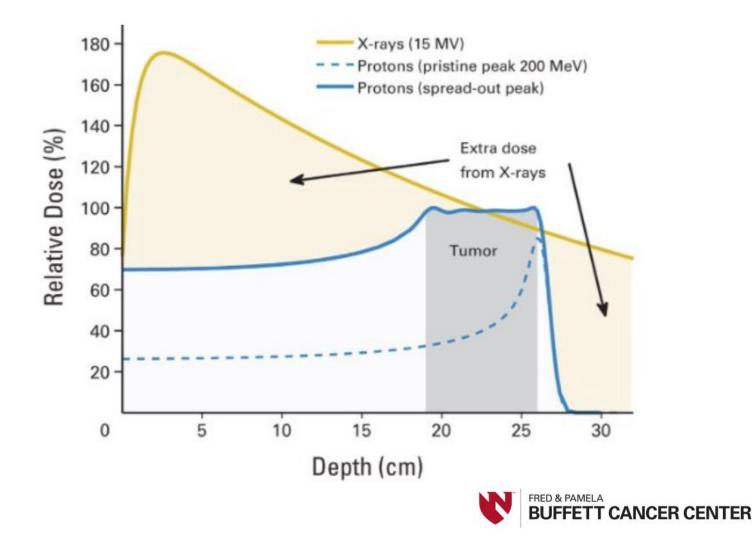
Childhood Cancers Rx with Proton Therapy

- Medulloblastoma
- Low and high grade gliomas
- Ependymoma
- Germ cell tumors
- Craniopharyngioma
- Atypical teratoid rhabdoid tumors (AT/RTs)
- Other rare brain tumors

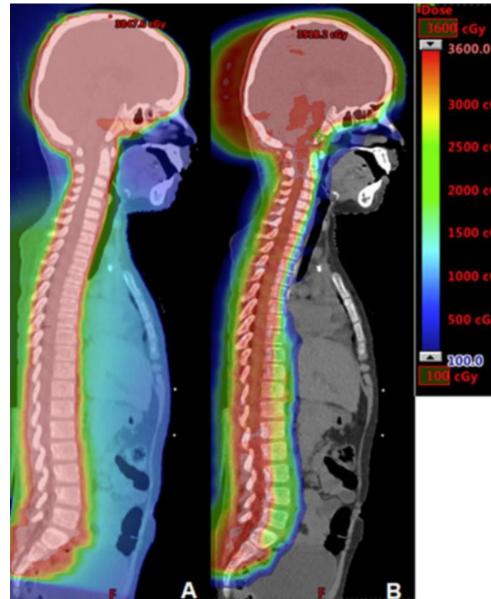
- Rhabdomyosarcoma
- Ewing sarcoma
- Other types of sarcomas
- Neuroblastoma
- Retinoblastoma
- Lymphoma, including Hodgkin
 lymphoma



Modified Proton Bragg Peak (Spread out Bragg Peak for Rx)



Craniospinal Radiation Therapy (X-Ray vs Proton Therapy)

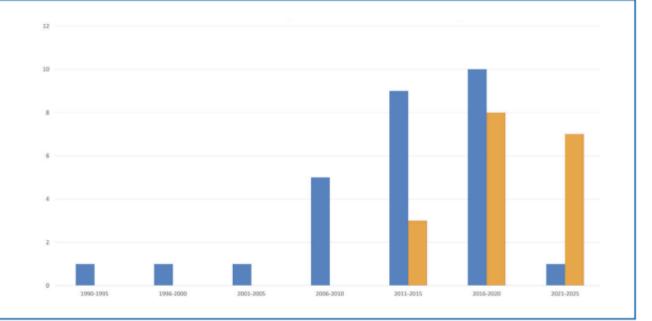




Most of the Proton Centers Being Built are Now Single Room Projects

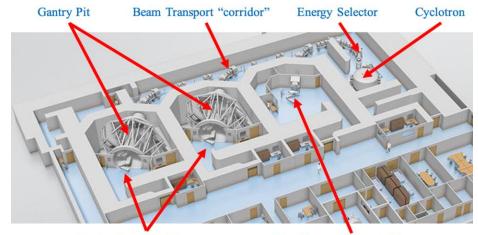
PROTON CENTERS DEVELOPED: MULTI CENTER VS. SINGLE ROOM

Smaller single room centers have dominated recent growth in proton therapy centers in recent years.



multi room single room

3 Treatment Room Proton Facility



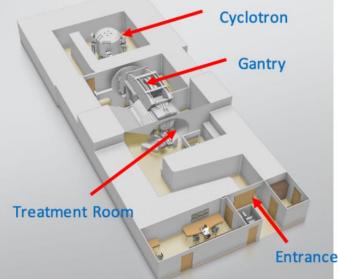
Gantry Treatment Rooms

Fixed Beam Treatment Room



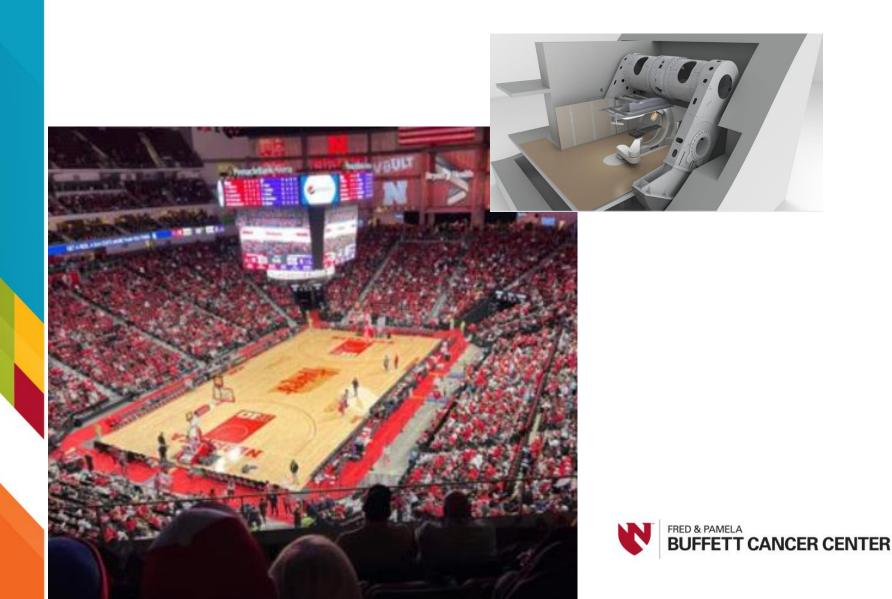
Compact Single Room Proton Facility (Full Court)







Compact Single Room Proton Facility (Half Court)



"Compact" Single Room Proton Facility (Half Court)







Fred & Pamela Buffett Cancer Center Varian Edge Linear Accelerator





Ultra Compact Single Room Proton Facility



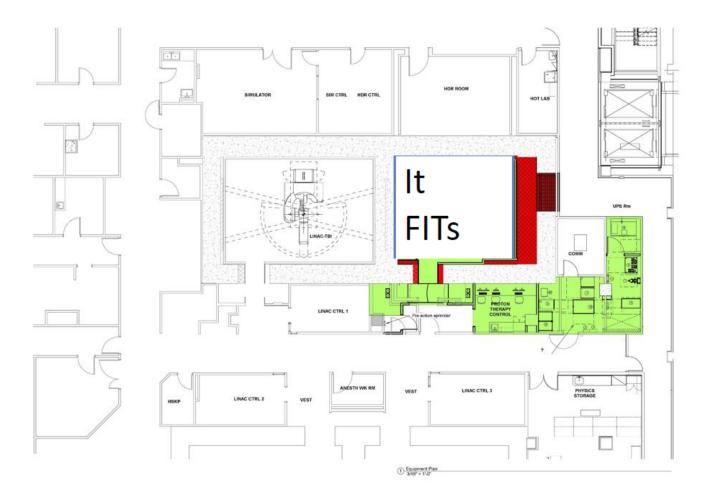


Mevion S250i FIT (Pending FDA Clearance Summer 2024)





Ultra Compact Single Room Proton Facility (Half Court)





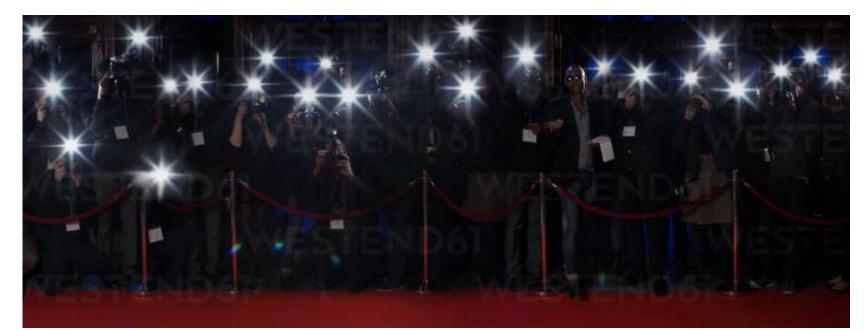
Mevion S250i FIT (Pending FDA Clearance Summer 2024)





FLASH Radiotherapy (FLASH-RT)







FLASH Radiotherapy

Treating tumors at ultra-high dose rate resulting in:

- 1. Reducing the effects of radiation therapy to normal tissue near the tumor target
- 2. While equaling the anti-tumor effect of conventional dose rate radiation therapy
- 3. Decreasing the side effects of radiation therapy to normal tissue could also allow for increasing the radiation dose to the tumor target



FLASH Radiotherapy

Dose Rate: Radiation Dose in Gy/second

1 Gy = 100 cGy = 100 RADs

Conventional Dose Rate: 0.017 Gy/second

FLASH DOSE RATE: >40 Gy/second

Typical FLASH Dose Rates: 140-166 Gy/second

FLASH-RT is >8000 times faster than Conventional-RT



How Does FLASH-RT Work?

- Depletion of oyxgen in normal tissue next to the tumor
- Less effect of FLASH-RT on the immune system

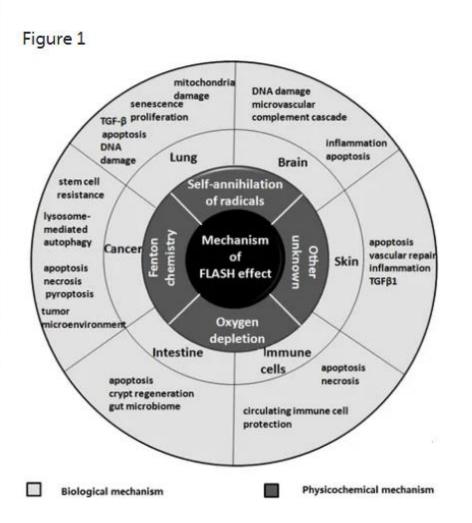


Figure 1 Themechanisms of FLASH effect.

Electron Flash Research UNMC

1st Electron Flash Beam on April 2, 2022

- Sumin Zhou, PhD Director Medical Physics Dept. Radiation Oncology
- Carson Cancer Center at Faith Regional Hospital In Norfolk NE
- Varian Medical Systems
- On April 2, 2022 measured electron Flash Beam at 188 Gy/second
- Cameras in the room captured a blue light in the experimental water tank used for Flash measurements. (Relativity!!!)



$E = mc^2$

(Energy = mass times the speed of light squared)

Energy & mass/matter are different but interchangeable



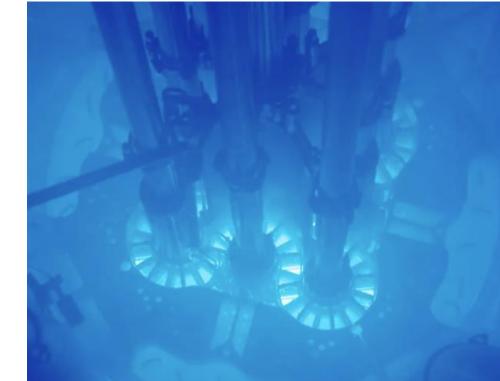
"*Now* that desk looks better. Everything's squared away, yessir, squaaaaaared away."



What if we accelerate matter beyond the speed of light?

When you accelerate a particle (ex. electron or proton) beyond the speed of light in water you convert matter to energy and see a blue light called

"Cherenkov Radiation"





First Patient Treated with FLASH-RT

- 75-year-old patent with a CD30+ T-cell cutaneous lymphoma
- Multiple different types of topical, PUVA, chemotherapy, radiation-Rx
- RT for 10 years, 20 Gy in 10 fx versus 21 Gy in 6 fx. Healing took 3-4 mos
- Received approval as the 1st human to be treated with FLASH-RT, 3.5 cm tumor
- 15 Gy delivered in 10 pulses over 90 milliseconds

Jean Bourhis et al. Radiotherapy and Oncology, Vol. 139, October 2019, Pages 18-22



1a : Day 0





1c:5 months

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Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

Human Trials with FLASH-RT are just starting

Electron FLASH is one option

Proton FLASH likely has the most potential

This is a very Hot Topic in Radiation Oncology





Thank You



