

PROSPER Study: A Comparative Effectiveness Trial of Surgery, Carbon Ion Radiotherapy, and Proton Therapy for Pelvic Sarcomas involving the Bone

**Bradford Hoppe MD, MPH
Professor of Radiation Oncology
Mayo Clinic, Florida**



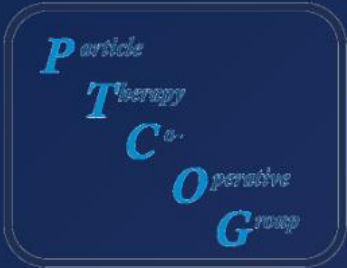
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Disclosures

I am employed by Mayo Clinic

I have no relevant financial relationships with ineligible companies to disclose, and I will include off-label or unapproved product usage in my presentation or discussions.

Why is the US interested in CIRT?



Particle Therapy Co-Operative Group

An organisation for those interested in proton, light ion and heavy charged particle radiotherapy

Particle Therapy Centers

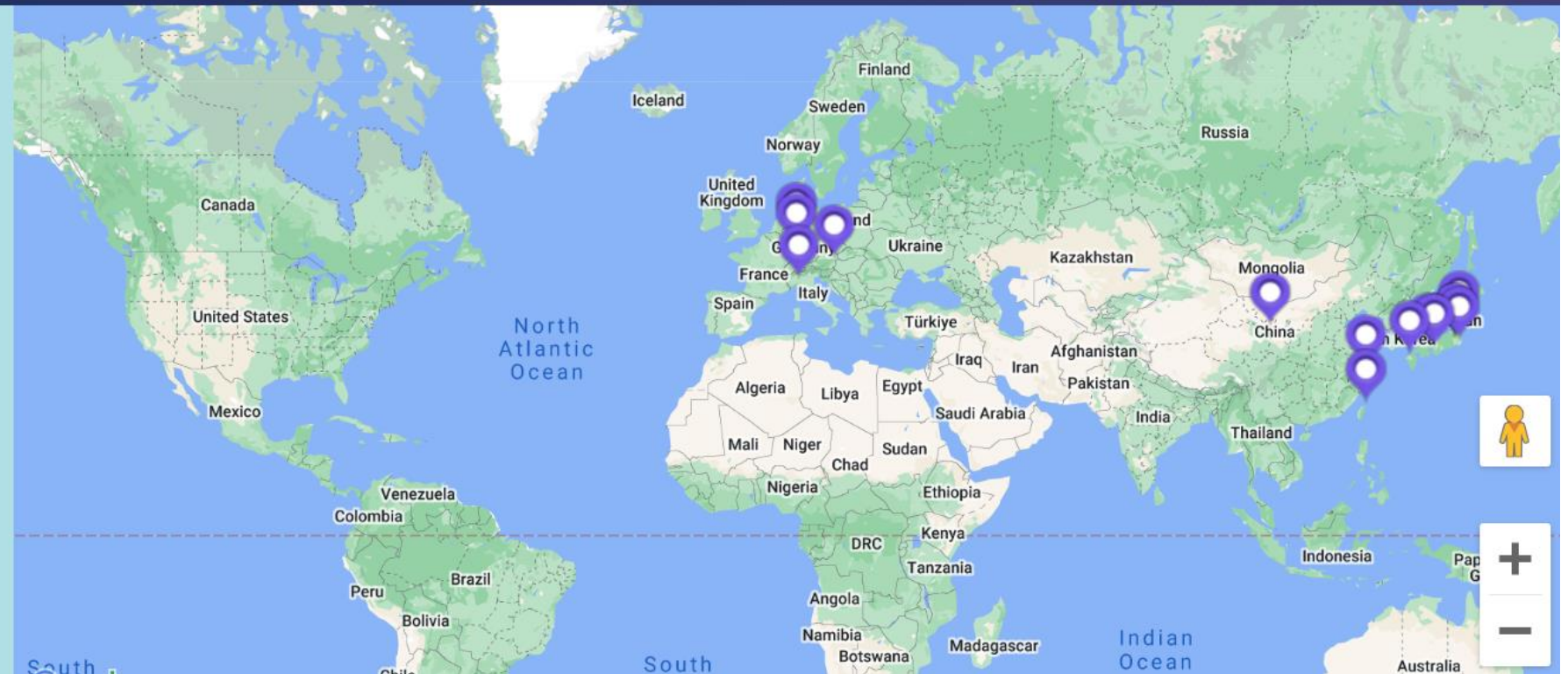
[Facilities in Operation](#)

[Facilities under Construction](#)

[Facilities in Planning Stage](#)

[Facilities World Map](#)

Clinical Practice



Why is the US interested in CIRT?

HEALTHCARE

Mayo Clinic in Jacksonville plans North America's first carbon ion therapy center to fight cancer

Matt Soergel msoergel@jacksonville.com

November 19, 2019

Published 6:32 a.m. ET Nov. 19, 2019

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This is a rendering of the integrated oncology facility planned for the Mayo Clinic's Jacksonville campus, which will include carbon ion therapy and proton beam therapy. [Provided by Mayo Clinic] *Florida Times-Union*

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2022

• Groundbreaking

2024

• IOB Opens (XRT)

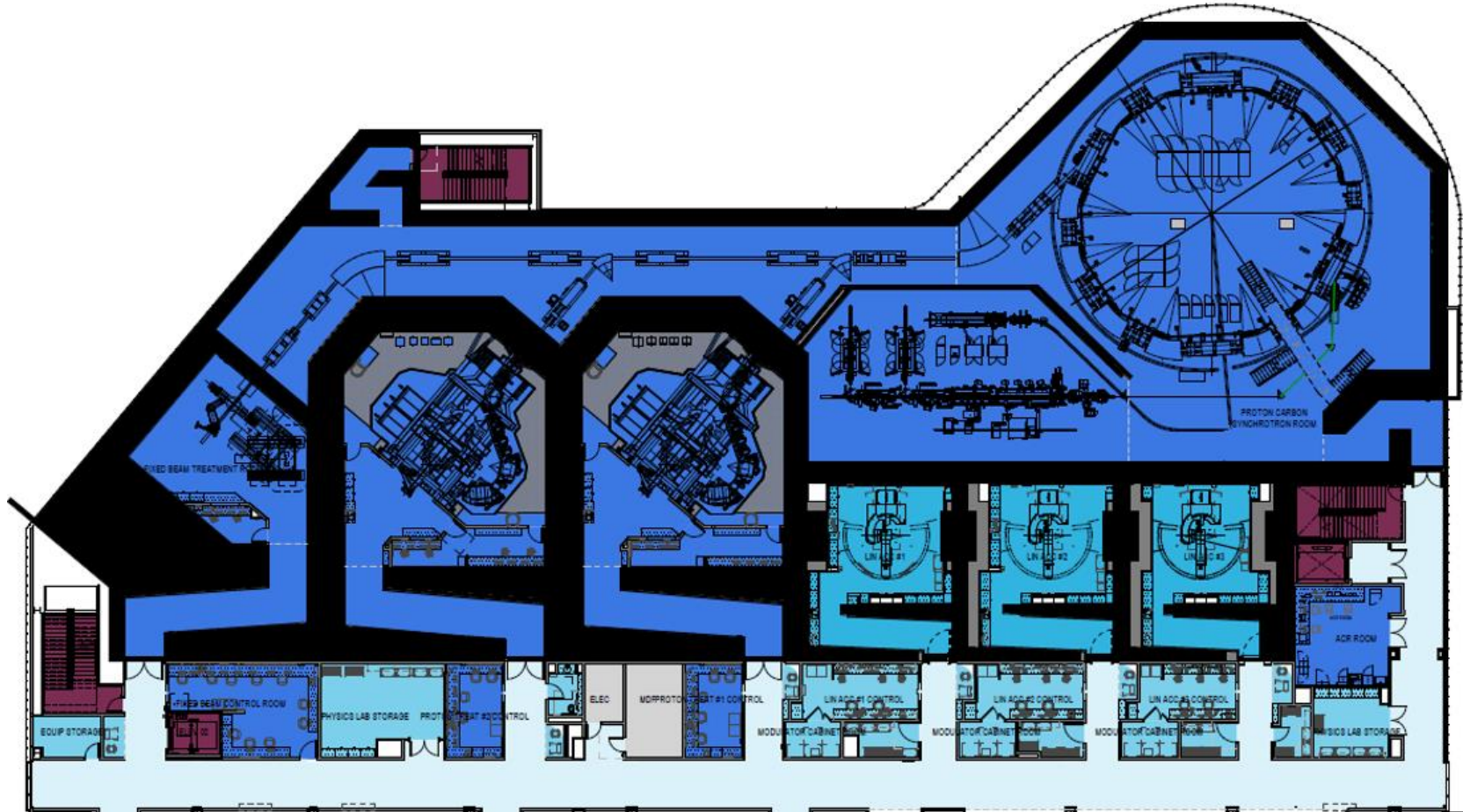
2026

• Proton ready

2027

• Carbon ion ready

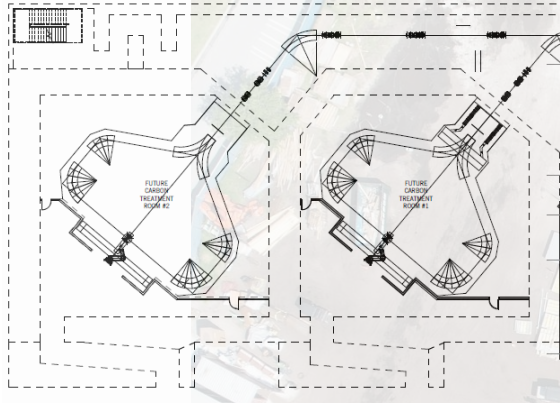
Integrated Oncology Building







Future CIRT Gantries?



Why a Clinical Trial on CIRT prior to 2027?

- Collaboration with international carbon ion centers
- Obtain experience with carbon ion therapy
- Develop evidence to help with FDA approval & reimbursement
- Develop infrastructure to conduct additional trans-continental CIRT trials

Clinical Trial 1.0- Pre-COVID

- Phase I trial (5-10 patients)
 - Evaluate ability of sending patients abroad (Europe/Asia) to successfully receive CIRT for radioresistant cancers
 - Locally recurrent rectal cancer
 - Non-squamous cell Head & Neck
 - Pelvic bone sarcomas
- Phase II trial (45 patients)
 - If Phase I is successful and funding secured, convert into 3 single arm Phase II studies (15 patients each)

Clinical Trial 2.0- COVID era



Clinical trial 2.0- What disease site?

- Address a cancer site, where there is little doubt that CIRT is critical

CIRT in pelvic bone sarcomas

- Systematic review found 18 publications– 60-70 GyE in 16 fxns
 - 5 Prospective studies (191 patients)
 - 13 Retrospective studies (almost 500 patients)

Author, Year, and Center	Histology	Study Design	No. of Pts.	Median Total Dose and/or Dose Range, GyE	Total Fxs	Median Follow-up, months (range)	Local Control Rate	Overall Survival Rate	Grade 3+ Toxicity or Other QOL Outcome
Matsunobu A 2012 NIRS ²¹	mixed	prospective phase 1/2	78	52.8 - 73.6	16	24 (2 - 166)	2 and 5 yrs, 73% and 62%	2 and 5 yrs, 58% and 33%	Acute: gr 3 skin reactions, 3 pts (4%) Late: gr 3 skin/soft tissue reaction, 4 pts (5%); gr 4 skin/soft tissue reaction, 3 pts (4%) Other: 4 pts with radiation-induced neurologic
Kamada T 2002 NIRS ¹⁸	mixed	prospective phase 1/2	57	52.8 - 73.6	16	21 (2 - 60)	1 and 3 yrs, 88% and 73%	1 and 3 yrs, 82% and 46%	Acute: gr 3 skin/soft tissue, 8 pts (14%) Late: gr 3 skin/soft tissue, 6 pts (11%)
Imai R 2011 NIRS ²⁰	chordoma	prospective phase 1/2	95	52.8 - 73.6	16	42 (13 - 112)	5 yrs, 88%	5 yrs, 86%	Acute: gr 3 acute skin reactions, 3 pts; Late: gr 3 late skin reactions, 2 pts; gr 4 late skin and soft tissue complications requiring skin grafts, 2 pts.
Imai R 2010 NIRS ¹⁹	chordoma	prospective phase 1/2	38	70.4 (52.8 - 73.6)	16	80	3 and 5 yrs, 95% and 89%	3 and 5 yrs, 95% and 86%	Acute: gr 3 acute skin reactions, 3 pts Late: gr 3 skin reactions, 2 pts; gr 4 reactions that required skin grafts, 2 pts; temporary or
Evangelisti G 2019 CNAO ²²	chordoma	prospective phase 1/2	18	70.4	16	23.3 (6 - 47)	PR, 10 pts (56.3%); SD, 5 (28.3%); LR, 2 (11%); DP, 1	2 yrs, 100%	Late: neuropathy, 8/18 pts (44%)

CIRT in Bone Sarcomas



National Comprehensive
Cancer Network®



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2022 Chordoma

PRESENTATION

PRIMARY TREATMENT

Sacrococcygeal
and
Mobile spine

Wide resection^b
± RT,^{c,d}
if resectable

OR

Consider RT^d
if unresectable

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Bone Cancer

Version 2.2022 — October 8, 2021



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2022 Bone Cancer

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PRINCIPLES OF RADIATION THERAPY

General Principles

- Patients should be strongly encouraged to have RT at the same specialized center that is providing surgical and systemic interventions.
- Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.

What Clinical Trial Design?

- Trial design that allows Mayo to contribute pts
 - Comparative effectiveness study
 - CIRT vs XRT/PT
 - CIRT vs surgery

CIRT > surgery in pelvic chondrosarcoma

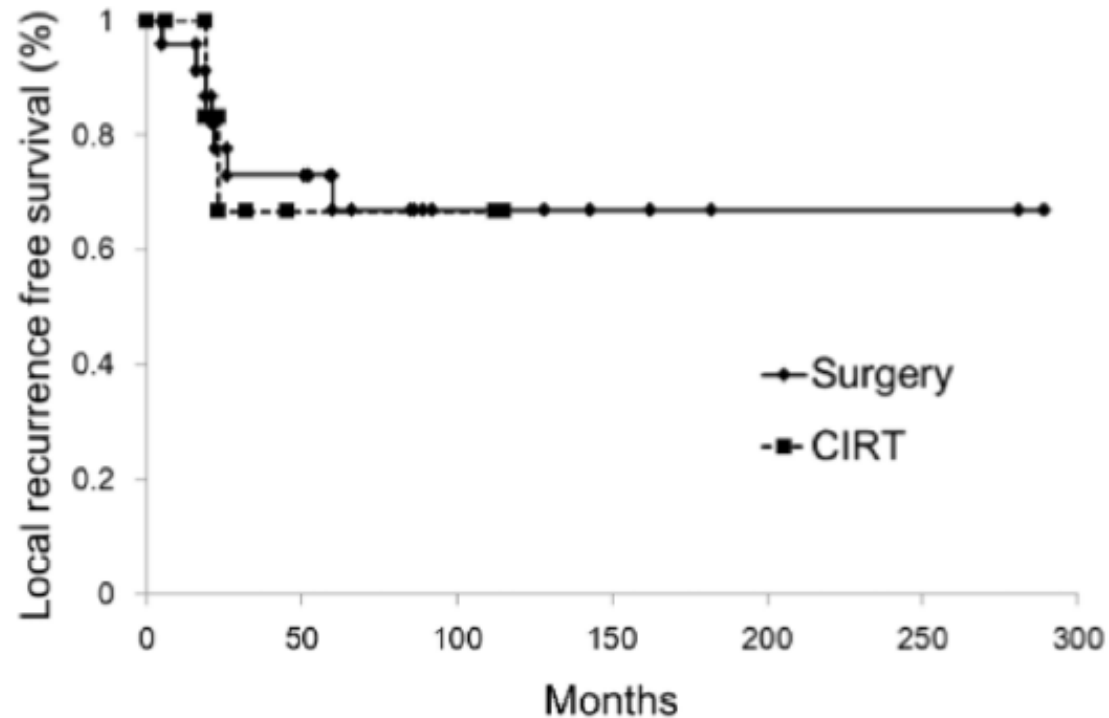


Table 3 MSTs functional evaluation scores in patients with periacetabular tumors

Treatment	No. of patients	Pain	Function	Emotional acceptance	Supports	Walking ability	Gait	Total score	Total score (%)
Surgery	10	3.9 (1.4)	2.2 (1.2)	2.9 (1.4)	1.8 (2.0)	2.9 (1.4)	2.6 (1.4)	14.9 (7.0)	49.6 (23.3)
CIRT	7	3.7 (0.8)	3.7 (1.0)	3.7 (0.5)	3.3 (1.7)	3.9 (0.7)	3.4 (0.5)	21.7 (3.5)	72.6 (11.6)

CIRT > Surgery or XRT in Sacral Chordoma

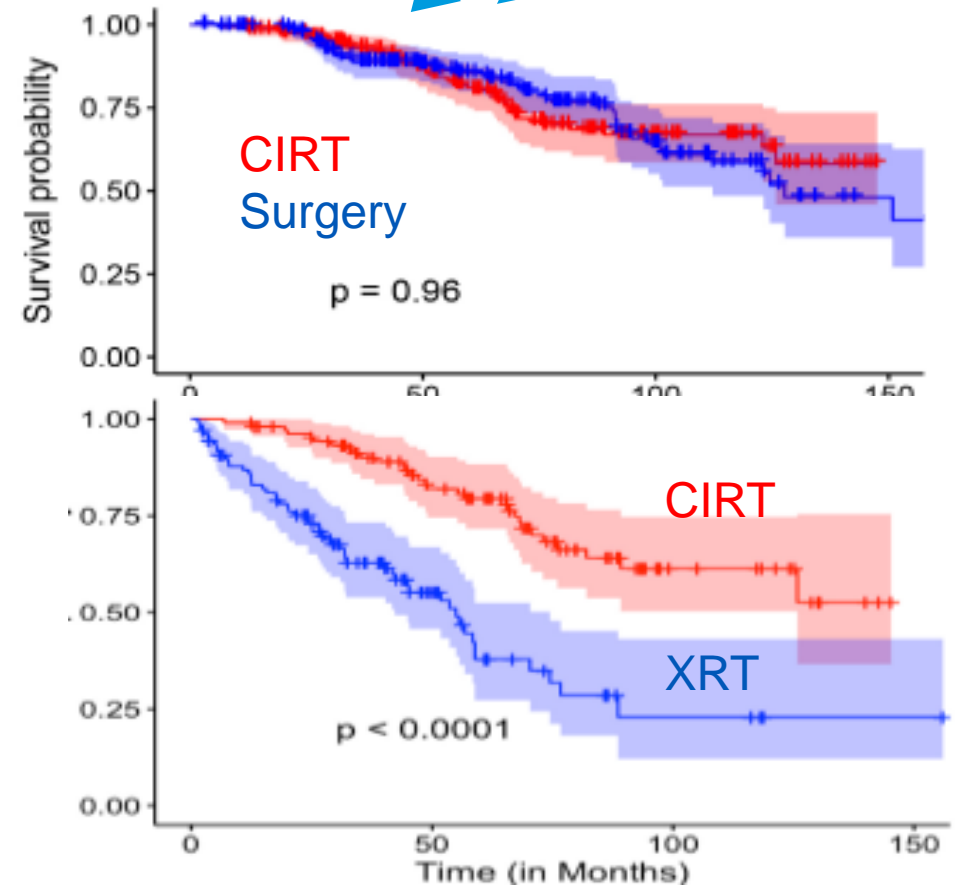
**MCR surgery
N=54**

**CIRT-QST
N=188**

**NCDB
N=669**

Table. CIRT vs En Bloc Resection Analysis

Outcome	HR or OR (95% CI)	P value
Cox proportional hazards		
Overall survival	0.71 (0.25-2.06)	.53
Progression-free survival	1.21 (0.61-2.42)	.59
Distant metastasis	1.44 (0.63-3.30)	.39
Univariate logistic regression		
Local recurrence	0.88 (0.31-2.41)	.80
Urinary retention	0.65 (0.26-1.57)	.34
Change in FMS score	2.41 (0.95-6.46)	.07
Peripheral motor neuropathy	0.13 (0.04-0.40)	<.001
Colostomy	0.78 (0.28-2.09)	.62



Carbon Trial in Bone Sarcoma

- Primary Endpoints
 - Quality of life & toxicity of CIRT compared with Surgery
 - Local Control of CIRT compared with proton/photon RT

How to ensure patients and centers will enroll?

- Pragmatic trial
 - Prospective cohort design, non-randomized (eg COMPPARE)
 - Few ineligibility criteria
 - Allow institutional variations in RT guidelines
- Minimal Risk study- everything is standard of care

Background- Carbon Trial

- Proposed concept to possible partners
 - QST Hospital
 - MedAustron
 - CNAO
 - SPHIC
 - University of Heidelberg
- Additional development with the partners

Enrollment

Eligibility criteria (N=108)
Age ≥ 15 y
ECOG PS score ≤ 2
Newly diagnosed disease
Nonmetastatic pelvic bone sarcoma
or soft tissue sarcoma involving
the pelvic bone(s)

Allocation

Treatment arm 1 (n=36)
CIRT delivered at centers in
Japan, China, Italy, Austria, and
Germany

Treatment arm 2 (n=36)
Surgical treatment with/without
radiotherapy (proton or photon) at
Mayo Clinic in Arizona, Florida,
and Minnesota

Treatment arm 3 (n=36)
Proton beam therapy at Mayo
Clinic in Arizona, Florida, and
Minnesota

Follow-Up

Follow-up at 3, 6, 12, 24, 36, 48, and 60 months
Medical history and physical examination
ECOG PS scores
Imaging of pelvis
PROMIS-29 and EORTC QLQ-CR29 questionnaires
Treatment sequelae
Anticipated lost to follow-up: n=6 per treatment arm, n=18 total

Analysis

Treatment sequelae
Local tumor control
Overall survival
Hospital length of stay

Inclusion criteria

- Males and females ≥ 15 years of age
- Newly diagnosed, histologic confirmation of pelvic chordoma, chondrosarcoma, osteosarcoma, Ewing sarcoma with bone involvement, rhabdomyosarcoma (RMS) with bone involvement or non-RMS soft tissue sarcoma with bone involvement
- No evidence of distant sarcoma metastases
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2
- **Patients capable of childbearing must agree to use adequate contraception.**
- Ability to complete questionnaire(s) by themselves or with assistance.
- Ability to provide written informed consent.
- Chemotherapy per institutional guidelines is allowed

Exclusion criteria

- Patients receiving palliative treatment
- Recurrent disease
- Males and females < 15 years of age
- Prior RT to the site of sarcoma
- Patients with distant sarcoma metastases
- Benign pelvic bone histologies

Statistics

- **Primary End Point:** Compare the difference in change of functional QOL from pre-treatment (baseline) to 1-year post-treatment between CIRT (Arm 1) and Surgery (Arm 2) (one-sided test for a two-sample t-test for independent means).
 - PROMIS 29 – physical functioning domain (4 questions)
 - Are you able to do chores such as vacuuming or yard work (1-5)
 - Are you able to go up and down stairs at a normal pace (1-5)
 - Are you able to go for a walk of at least 15 minutes? (1-5)
 - Are you able to run errands and shop? (1-5)
- Expect an average decline of functional QOL from CIRT of 2 points while surgery will decline 4.6 points (higher than defined minimal clinically important difference [MCID]) with equal standard deviation of 4 points.
- 80% power ($\alpha = 0.05$) to detect significantly improved functional QOL from CIRT over surgery with 30 patients per treatment arm.

No difficulty
Little difficulty
Some difficulty
Much difficulty
Unable to do

Statistics

- **Secondary End Point:** Evaluating local control between carbon ion therapy and proton therapy at 3 years.
 - Analyses of local control will be:
 - stratified by histology
 - subset analyses (sacral chordomas vs. non-sacral chordoma histologies)
 - The proportion of patients experiencing local control at 3 years will be calculated along with 95% confidence intervals with a one-sided test for non-inferiority to be conducted between the PT and CIRT arms.
- **Exploratory End Point:**
 - Local control- CIRT vs surgery
 - CTCAE Toxicities
 - PROMIS QOL
 - EORTC- CRC Q29

Radiation Treatment -- Pragmatic

- Target Volumes
 - Per treating institution standards
- Dose-fractionation
 - Per treating institution standards
- RBE model for CIRT (LEM, MKM, other?)
 - Per treating institution standards
- Plan to collect DICOM files of the RT plans centrally after completion of treatment and will review retrospectively

Trial Infrastructure

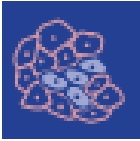
- Funding from MCF & MCE Cancer Center
- MC research is overseeing patients treated at MCF, MCA, MCR
- Contracted with a Clinical Research Organization (CRO)- ICON
 - Provide administrative support for opening the trials at centers in Europe & Asia
- Paying case-based rate to the institutions for enrolling patients
- Redcap database

Prosper Timeline

- January 20, 2022- MCF opened trial
- February 14, 2022- MCA opened trial
- June 1, 2022- MCR opened trial
- May 2023- First patient enrolled (MCF- surgery)
- September 2023- Open at European and Japan sites
- Finish accrual 2026 to all 3 arms









Challenges

- Rare tumor trials can be difficult to accrue
- International trials are challenging administratively
- Value of a CRO for research assistance?
- CIRT RBE model (LEM vs MKM)
- Surgical patients likely have smaller, less invasive tumors



Study Protocol

Pragmatic, Prospective Comparative Effectiveness Trial of Carbon Ion Therapy, Surgery, and Proton Therapy for the Management of Pelvic Sarcomas (Soft Tissue/Bone) Involving the Bone: The PROSPER Study Rationale and Design

Bradford S. Hoppe ^{1,*}, Ivy A. Petersen ², Benjamin K. Wilke ³, Todd A. DeWees ^{4,5}, Reiko Imai ⁶ , Eugen B. Hug ⁷, Maria Rosaria Fiore ⁸, Jürgen Debus ^{9,10}, Piero Fossati ^{7,11}, Shigeru Yamada ⁶ , Ester Orlandi ⁸, Qing Zhang ¹² , Cihang Bao ¹², Katharina Seidensaal ^{9,10}, Byron C. May ¹ , Anna C. Harrell ¹ , Matthew T. Houdek ¹³ , Laura A. Vallow ¹, Peter S. Rose ¹³, Michael G. Haddock ², Jonathan B. Ashman ⁵, Krista A. Goulding ¹⁴, Steven Attia ¹⁵, Sunil Krishnan ¹⁶ , Anita Mahajan ², Robert L. Foote ² , Nadia N. Laack ², Sameer R. Keole ⁵, Chris J. Beltran ¹, Eric M. Welch ², Mohammed Karim ¹³ and Safia K. Ahmed ⁵

Thanks!

QST Hospital

Reiko Imai
Shigeru Yamada

MedAustron

Eugen Hug
Piero Fossati

CNAO

Maria Rosaria Fiore
Ester Orlandi

SPHIC

Qing Zhang
Cihang Bao

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Katharina Seidensaal

MCR

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