In Vivo Prompt Gamma-Ray Spectroscopy for Personalized, Adaptive Particle Radiation Therapy of Bone Cancer

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PGS to Adaptation

Concept – What?
A novel in vivo method to monitor bone cancer during particle therapy that uses prompt gamma-ray spectroscopy to quantify calcium (Ca) mass density in bone.

Calcium Signature – How?
Upon beam irradiation with a particle beam, Ca specific gamma emissions are induced by inelastic nuclear reactions. Interfractional monitoring of these Ca related signatures may provide personalized, quantitative metrics of bone treatment response.

Adaptive Therapy – Clinical Impact
These data can support adaptive therapy decision-making and trigger follow-up assessment or replanning as needed, without any additional radiation exposure beyond the therapeutic beam.

Introduction

Metastatic bone disease is a major complication of advanced cancer, causing pain, pathological fractures and reduced quality of life [1, 2]. Modern particle therapy enables highly conformal treatment of radioresistant tumors. However, disease- and treatment-related changes in bone mineral density remain difficult to monitor [3, 4].

This work aims to develop the first patient-like platform for investigating the relationship between bone calcium mass density and the prompt gamma-ray spectroscopy (PGS) response during particle therapy. To establish PGS as a quantitative treatment-monitoring method, the study follows three connected steps:

1. **Bone-scaffold development**
   – Develop bone-like scaffolds with controlled calcium content, density and porosity for experimental and computational validation.
2. **Experimental identification of Ca-specific PG lines**
   – Perform PGS measurements to identify and characterize Ca specific prompt gamma-ray (PG) emission.
3. **Prediction of calcium mass density**
   – Use Monte Carlo (MC) simulations to investigate how Ca specific PGs can be used to quantify Ca mass density.

1. Bone-Scaffold Development

- Gammex™ 467 tissue-equivalent inserts with known density (ρ) and Ca mass density ($\rho_{Ca} = \rho w_{Ca}\ [gcm^{-3}]$) were used as reference materials.
- β-TCP/ClaroFast based bone scaffolds with controlled Ca were produced.

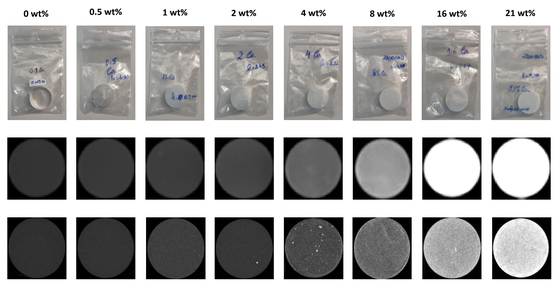

Figure 1. β-TCP scaffolds with controlled Ca content: photos (top), PCCT images (middle), micro-CT images (bottom).

- Photon-counting CT (PCCT, at 120 kVp) and micro-CT (at 65 kVp) were used to evaluate the HU response of the fabricated materials as a function of ρ and ρ_{Ca}.

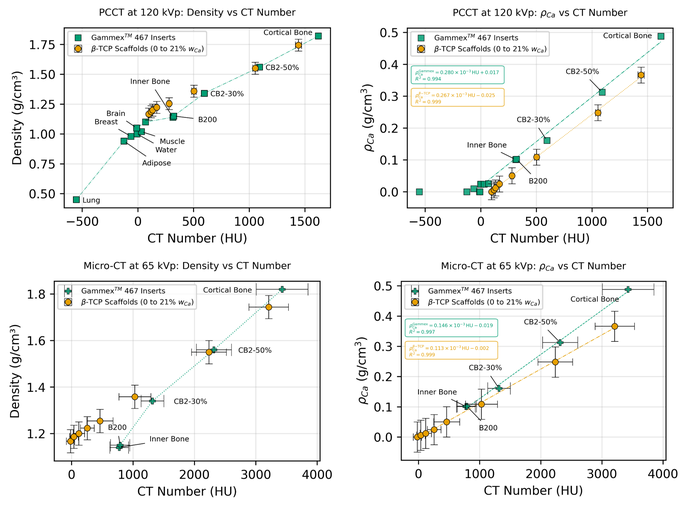

Figure 2. Material density and Ca mass density as functions of HU for Gammex™ 467 reference inserts and β-TCP scaffolds measured with PCCT and micro-CT.

Engineered β-TCP showed predictable CT responses as a function of ρ and ρ_{Ca}, with HU increasing linearly with ρ_{Ca}.

2. Experimental Research
Identification of Ca-Specific PGs

- Experimental Setup at Marburg Ion Therapy Center (MIT):
  – Spectroscopic unit: $CeBr_3$ + BGO (AC-Shield) + DAQ (FlashCam);
  – Proton beam: 50 MeV at clinical intensities;
  – Target: CaO.

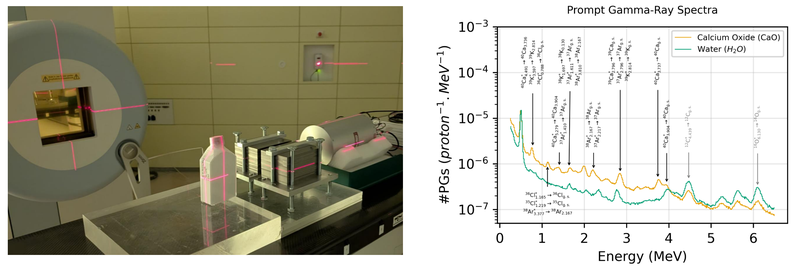

Figure 3. Experimental setup and resulting prompt gamma-ray spectra for the irradiation of calcium oxide and water with 50 MeV protons. Ca lines from proton-induced inelastic nuclear reactions are indicated in black, with main carbon and oxygen lines shown for reference in gray.

Proton beam irradiation revealed distinct Ca related PG lines, providing the spectral basis for Ca mass density quantification.

3. Monte Carlo Research
Prediction of Calcium Mass Density

- MC simulations in Geant4 with a single spot proton beam of 50 MeV irradiated cylindrical scaffold-like phantoms.
- A $CeBr_3$ detector with an anti-coincident logic was modeled, including its energy resolution and response, to record the prompt gamma-ray spectrum.
- Ca controlled materials samples served as training set, while Gammex™ 467 tissue-equivalent inserts served as testing set.

The Multiple-Peak Fit Model

– Developed by quantifying the areas of the main PG peaks.

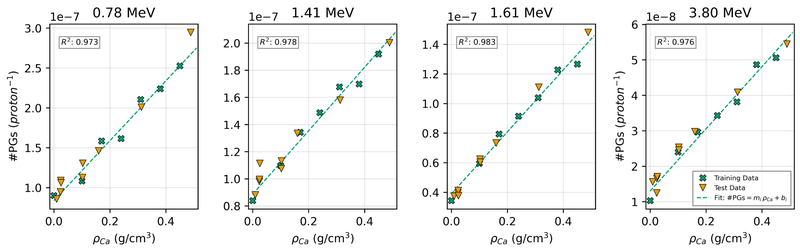

Figure 4. Example of Ca specific prompt gamma-ray (0.78, 1.41, 1.61 and 3.80 MeV) yields as a function of Ca mass density, with linear fits to the training data.

Final Output: ρ_{Ca} Estimation

– Individual estimates were combined via weighted fusion into a single Ca prediction to improve robustness over any single line.

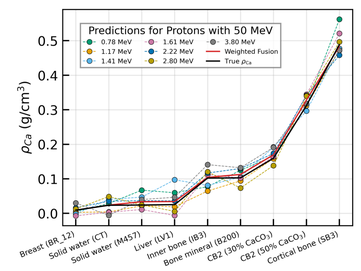

Figure 5. Predicted vs ground truth Ca mass density for Gammex™ 467 tissue-equivalent inserts.

Table 1. Performance metrics for Ca mass density predictions based on individual CA specific PGs and weighted multi-peak model.

PG Peak (MeV)	MAE (g cm⁻³)	RMSE (g cm⁻³)	Max. Error (g cm⁻³)
0.78	0.0238	0.0326	0.0732
1.17	0.0109	0.0157	0.0375
1.41	0.0229	0.0298	0.0719
1.61	0.0178	0.0211	0.0322
2.22	0.0175	0.0194	0.0304
2.80	0.0169	0.0197	0.0294
3.80	0.0231	0.0250	0.0389
Model	**0.0065**	**0.0078**	**0.0116**

Sub-1 wt% Ca prediction error.

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