Introducing uncertainty in measurement based assessment of relative biological effectiveness in carbon ion radiotherapy

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INTRODUCTION

Carbon ion therapy is a novel modality used for the treatment of tumors that are unresectable, close to critical structures, or resistant to standard radiotherapy. This includes treatment or pancreatic cancer, which is largely untreatable with current radiotherapy (i.e., x-rays), and is the 3rd leading cause of cancer related death in the US. However, the potential of carbon ions is untested. In order to obtain consistent outcomes in radiation therapy, the dose must be delivered within 5% of the desired value. To conduct clinical trials and compare patient outcomes, uncertainties, including in RBE, should be **less than 5%**. One of the largest inconsistencies in dose delivered during carbon therapy is in RBE, a value that is calculated via one of several recognized algorithms.

$$RBE = \frac{D_{ref}}{D_{exp}}$$

This study investigates the uncertainties in measured microdosimetric input parameters for RBE estimates by three models, MKM, RMF, and LEM I. As all physical measurements are inherently subject to various sources of uncertainty, the addition of noise into the microdosimetric spectra is essential to ensure the accuracy of clinical RBE. Eight unique sources of uncertainty anticipated to affect the physical beam measurements have been identified using ICRU Report 36[2]. Each source was quantified and added to the Monte Carlo simulations independently, to quantify each sources through lineal energy values. Additionally, the uncertainty in estimating the RBE using microdosimetric parameters was assessed for RMF and LEM I.

Aim:

1. Calculate and extract input parameters for each RBE algorithm from Monte Carlo based microdosimetric spectra over a range of clinical beam energies.
2. Quantify and introduce each of eight unique sources of noise into lineal energy spectra to evaluate their impact on calculated values and quantify physical measurement based uncertainty.

METHOD

Microdosimetric spectra were calculated using Monte Carlo (GEANT IV) for monoenergetic carbon beams of clinical energy. From these spectra, both dose and frequency mean lineal energy values were calculated as functions of initial beam energy and depth for clinically relevant beam energies. Kinetic energy spectra was also calculated for each contributing fragment. These values were used to calculate RBE based on 3 recognized algorithms, MKM, RMF, and LEM I. The impact on the RBE from eight unique sources of uncertainty associated with Tissue Equivalent Proportional Counter (TEPC) measurements were simulated.

Sources of uncertainty[2]:

1. Electronic Uncertainty
2. Gas Pressure
3. W-value
4. Gain Instability
5. Low Energy Cut-off
6. Counting Statistics
7. Pulse Pile-up
8. Wall Effects

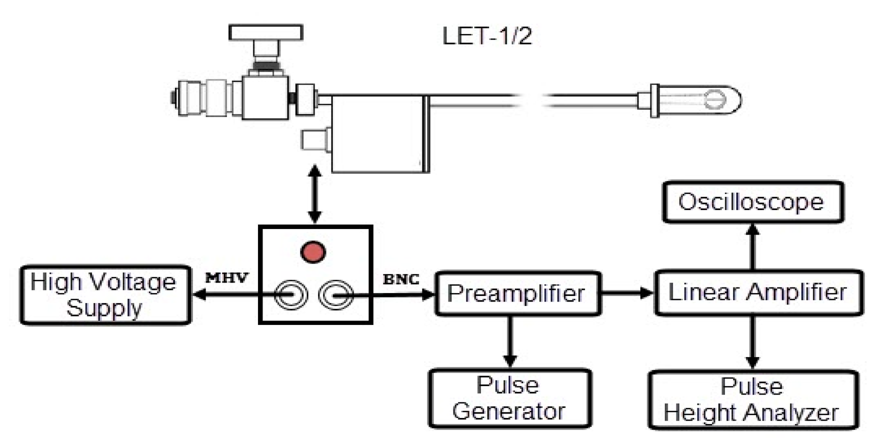


Figure 2. Diagrams the TEPC used for this study, the LET-1/2, along with the corresponding electronics. This setup was assessed as part of the uncertainty analysis.

Measurement Based Uncertainty:

These sources were quantified by statistically introducing uncertainty into the simulated measurements 200 times and sampling the resultant RBE (associated with each of the 200 perturbations). A MatLab program was written in which noise was systematically added in a Gaussian or Poisson method over 200 iterations, the process of which follows:

- At each iteration, the spectra was shifted based on the uncertainty distribution
- Lineal energy values were recalculated using the shifted spectrum for each iteration
  - Result: matrix of 200 different lineal energy values
- RBE recalculated according to each different model
  - Result: 200 RBE values as a function of depth, beam energy, and RBE model
- Standard deviation of these 200 values were used to form error bars for the measurement due to each source of uncertainty
- Standard deviation added in quadrature to form overall margins for the RBE value

RBE Estimation:

RBE was estimated for RMF and LEM I models based on the microdosimetric quanitity, saturation corrected dose mean lineal energy, as this is the input to MKM calculations and can be measured using a TEPC. The estimation was made by fitting alpha and beta values of carbon as functions of y* for several test beam energies. These fits were then used to calculate alpha and beta based on y* for a set of validation energies, to quantify the uncertainty in the final estimations.

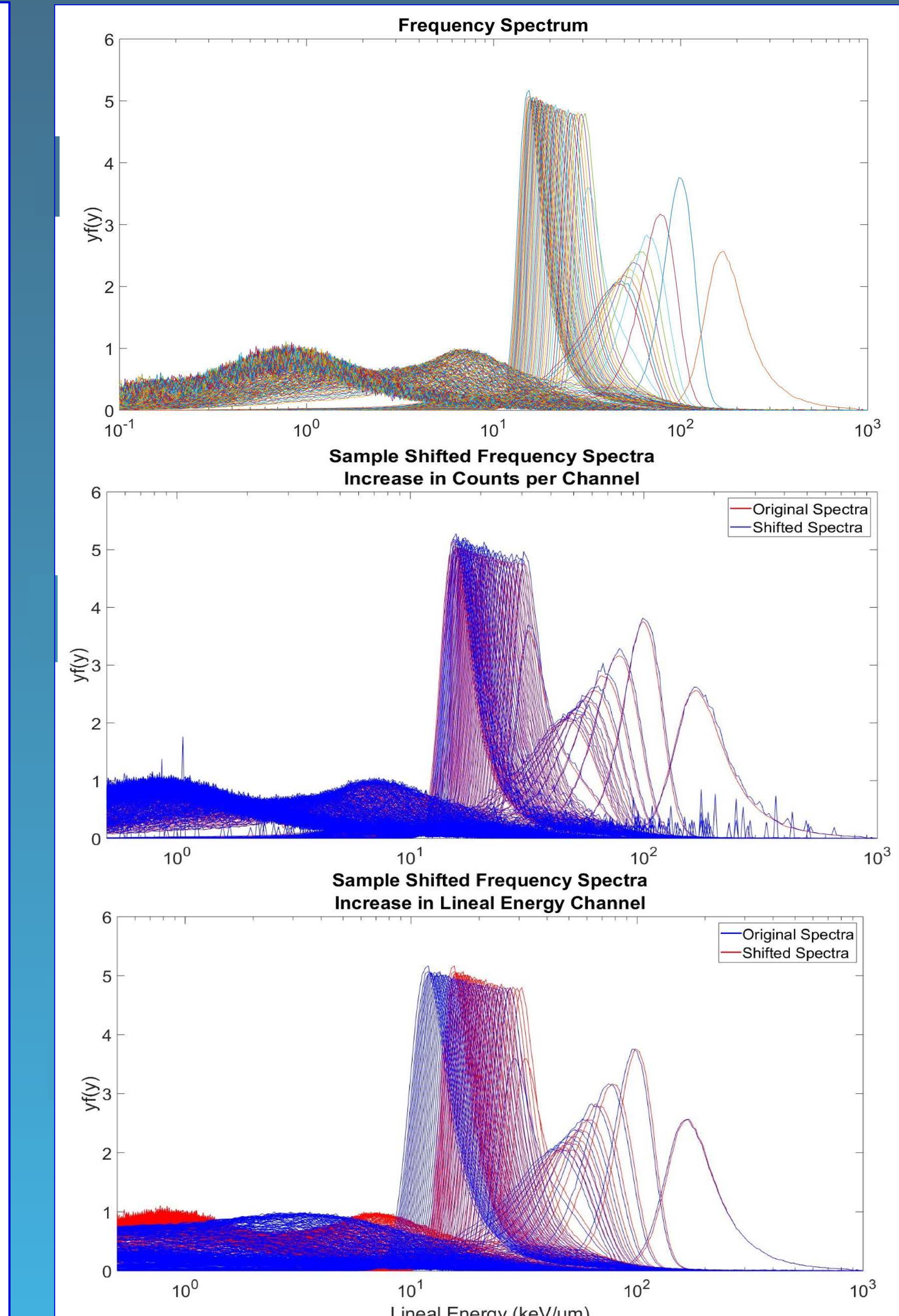


Figure 3. Displays the frequency spectrum of a 146 MeV/u frequency weighted microdosimetric distribution (top). The middle and bottom distributions show the spectra shifted in number of counts per channel and in lineal energy, respectively.

CONCLUSIONS

The overall uncertainty in RBE was typically less than 3% and was, at most, 4.0% (1-sigma). While the true RBE has extensive uncertainty associated with it, the modeled RBE can be measured with good accuracy, within a 5% deviation, which is tolerance reasonable goal for assessing delivered dose, according to the typical standards for radiation therapy.

FUTURE DIRECTIONS

- Purchase the LET-1/2 and make measurements with which to test and validate the uncertainty calculations
- Test further ways with which to validate the measurement based system
  - TLD, OSLD, Film etc.

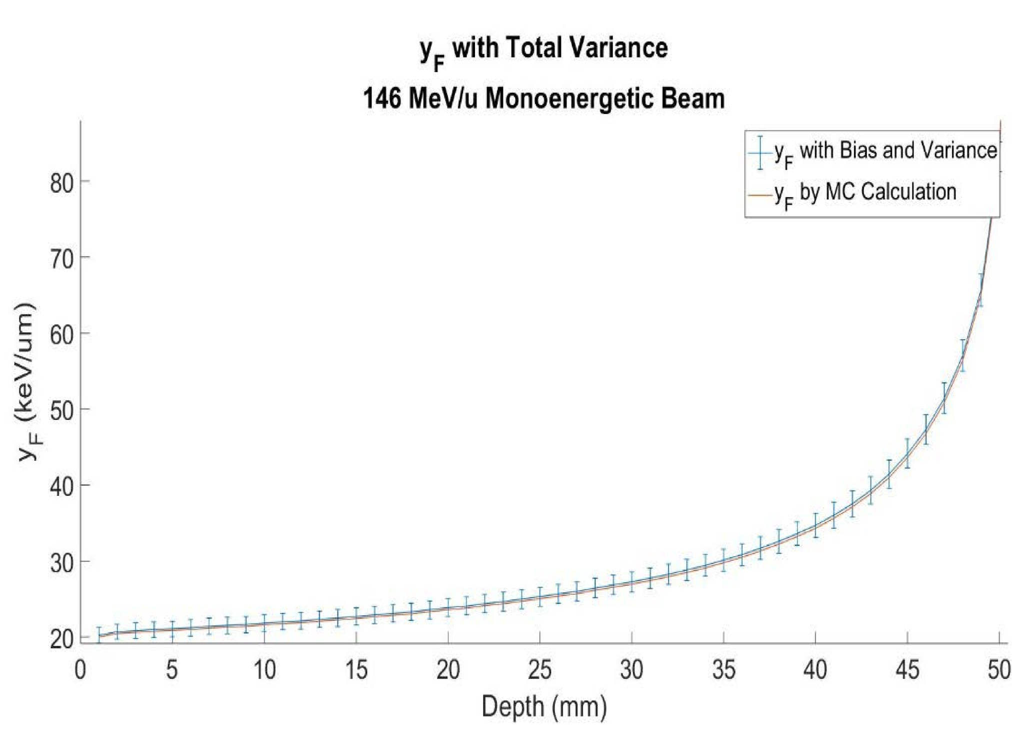
REFERENCES

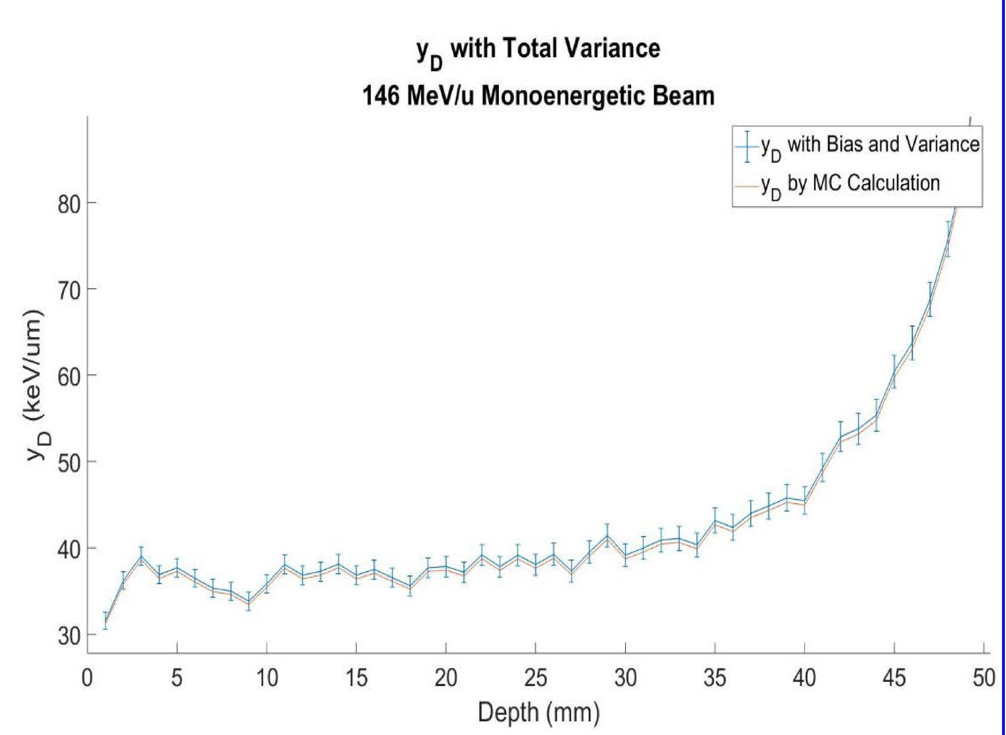
1 Nobuyoshi Fukumitsu, "Particle Beam Therapy for Cancer of the Skull Base, Nasal Cavity, and Paranasal Sinus," ISRN Otolaryngology, vol. 2012, Article ID 965204, 6 pages, 2012. https://doi.org/10.5402/2012/965204.

2 (1983). Microdosimetry. ICRU Report. I. C. o. R. U. a. Measurements. Bethesda, MD. **36:** 35-36.

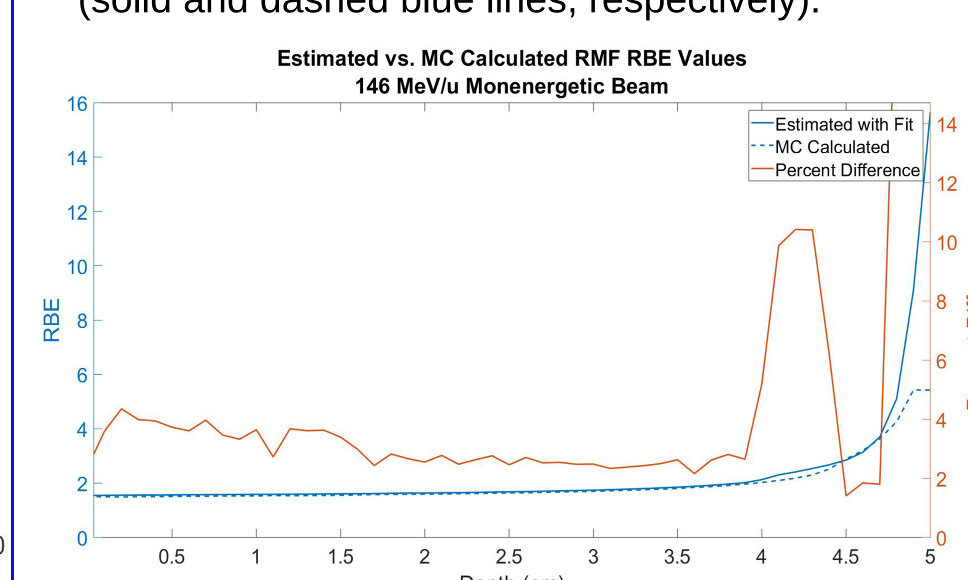
RESULTS

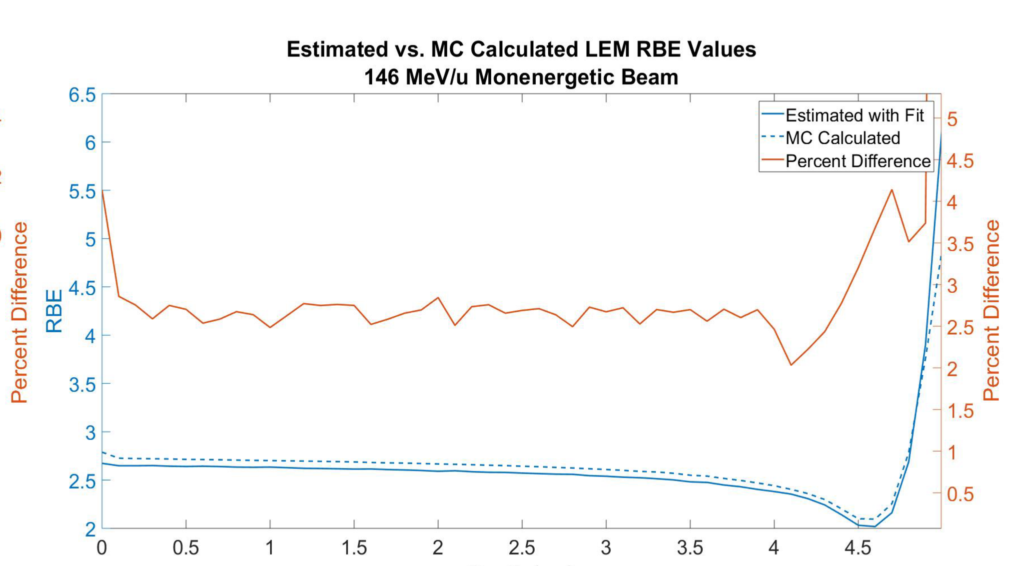
The plots to the right show the uncertainty introduced into lineal energy values based on each of the eight sources of physical noise assessed. Each error bar represents the 1-σ standard deviation introduced into the value.





The plots below show the error introduced into RMF and LEM I by method of estimation from y* values in the form of percent difference (orange line, right axis scale) between estimated and MC calculated values (solid and dashed blue lines, respectively).





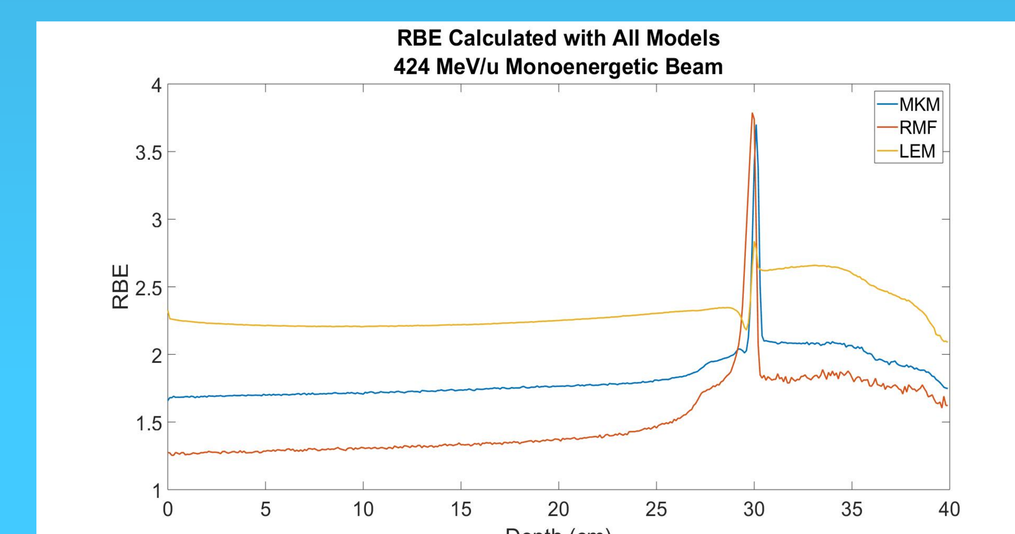


Figure 4. Shows the RBE calculated by each model, without uncertainty, for a 424 MeV/u monoenergetic carbon beam. Physical dose is displayed in orange for a comparison with the depth dose distribution.