Development and Validation of Precision in Small Animal Radiotherapy Dose Monitoring

by

Bria Moore

Graduate Program in Medical Physics
Duke University

Date: __________________________
Approved: __________________________

Terry Yoshizumi, Supervisor

Joseph Lo, Chair

Oana Craciunescu

Rathnayaka Gunasingha

David Kirsch

Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate Program in Medical Physics in the Graduate School of Duke University

2018
ABSTRACT

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Abstract

Commercial x-ray irradiator units for small animal irradiation in preliminary cancer studies have become common in radiobiology research. As institutions and researchers acquire new equipment that is simpler to use, x-ray units are typically operated by users without supervision and physics support following initial set-up and training by manufacturers. However, experiments can have widely varying methods of set-up, calibration, and dosimetry. This has led to a documented lack of reproducibility in a variety of small animal studies. A primary contributing factor in this is the lack of standardization of dose delivery in small animals. It has been noted that in some cases the extreme steepness in radiobiology response curves can lead to a change in biological response from 5% to 90% levels with a variance in dose of 10%. Large scale studies that compare dose deliveries at several sites aim to describe a clear picture of the role of inaccurate dosimetry in the documented lack of reproducibility in preclinical studies. Small animal dosimetry is typically simplified into a single look-up table tabulated by device manufacturers or institutional physics groups.

Thermoluminescent dosimeters (TLDs), specifically TLD-100 LiF chips, are generally accepted as the gold standard in kV x-ray dosimetry for small animal studies and these types of large scale projects. However, it is equally well known that these dosimeters require specific calibrations to convert light output to dose. Many
comparison studies use half value layer (HVL) measurements to match TLD calibration curves to dose measurements. The dissertation will determine the appropriateness of the use of HVL as a normalizing factor for polychromatic x-ray beams.

In addition to current dosimeter technology, our laboratory developed a novel dosimeter (Nano-FOD) that uses the combination of an organic scintillator pellet and a fiber optic technology to measure dose in real time. The scintillator pellet is composed of Europium-doped yttrium oxide which was demonstrated to have improved stimulated light production in nano-particle form vs. its bulk form, so the material was adapted for our application. To expand to new applications, such as organ-specific in vivo dosimetry for small animals, several physics characteristics have been investigated to inform us of the detector’s expected behavior.

Since TLDs are known to have slight differences in response based on batch and manufacturer date, three TLD batches from our institution that had been routinely used in kV x-ray applications were acquired. Batches were purchased between 2003 and 2011. Each batch was exposed at 5 different kVp values: 135, 150, 200, 250 and 320. At each kVp, the HVLs with matching filtration (2.5 mm Al + 0.1 mm Cu) as well as the necessary filtration to match the HVL at varying kVp values within ±5% was measured. The TLDs were exposed to these beams with matching beam filtrations as well as HVL-matched beams and measured calibration curves in each beam. A linear least-square fit was applied to each calibration curve and all $R^2$ values were greater than 0.97. There was
no correlation found between HVL and calibration slope in any of the three batches. 

With this information, it was determined that calibration curves from HVL matching in broad spectrum beams, such as those used in small animal irradiators, can lead to dose discrepancy of up to 300% at a true dose of 200 cGy. There was less variation between doses at lower energies, such as 135 and 150 kVp. In higher energy beams, there is a larger contribution of photons at characteristic energies. To minimize dose errors, the results of this study lead us to conclude that it is necessary to match both HVL and kVp to achieve an accurate dose calibration curve for TLD-100 chips.

Our institution dosimetry protocol calls for both HVL and kVp matching inherently since calibration and exposure are usually taken in identical beams. To confirm the accuracy of our current methodologies, our x-ray irradiator and filters were recreated in the FLUKA advanced interface (flair). By modeling one of our small animal plexiglass phantoms, dose deposited in TLD dosimeters placed centrally in the phantom was calculated. These doses were compared to measured dose from TLDs and the nano-FOD. Doses agreed to within 1% between Monte Carlo and nano-FOD.

The nano-FOD has current applications in high dose rate (HDR) brachytherapy, micro beam radiation therapy and x-ray dosimetry. Previous studies determined the angular dependence, lifetime radiation effects and linearity of the dosimetry. In this dissertation, data was compiled on temperature dependence and the detector energy response in orthovoltage and megavolt (MV) x-rays. At temperatures between 5 and 46
C, the detector response fell within ±5% of the mean value. An appropriate, distance-based calibration methodology for MV x-rays that address the energy dependence of our detector was determined. These characteristics allowed us to explore other applications of the nano-FOD technology.

A clinical trial in external beam radiation therapy (EBRT) was designed to test the feasibility of using our real-time nano-particle fiber optic detector (nano-FOD) in clinical EBRT treatments. Prior to patient accrual, the detector system was enhanced with improved Cerenkov subtraction via a dual fiber system to complete preliminary calibration. To calibrate our detector, a depth-dependent calibration method using beam data tables for comparison was developed. In phantom studies, overall dose agreement to fell within 5% using this calibration curve.

In patient studies, the nano-FOD was used to measure skin dose during various types of EBRT treatments including intensity modulated radiation therapy (IMRT) and volumetric arc modulated radiation therapy (VMAT). Accrued patients were being treated for a variety of malignancies in a number of areas on the chest and lower abdomen/pelvis. All nano-FOD measurements were compared to calculated values from the clinical treatment planning system (TPS). To date, a total of 15 patients have been accrued for grand total of 56 measurements. Overall percent difference was calculated to be around 10%. In addition, the effects of bolus were investigated in this study. Bolus is used to boost skin dose and in patients were bolus was used improved accuracy to
within 6% was observed. The nano-FOD is concluded to provide a viable option for skin dose monitoring in EBRT and our calibration methodology is effective in this application.
Dedication

This document is dedicated to my strong, patient, motivating, and wise mother.
## Contents

Abstract ................................................................................................................................. iv

List of Tables .......................................................................................................................... xv

List of Figures ........................................................................................................................ xvi

List of Abbreviations and Symbols ...................................................................................... xix

Acknowledgements ............................................................................................................... xxi

1. Introduction ....................................................................................................................... 1

   1.1 Background .................................................................................................................. 1

   1.2 Small Animal Dosimetry ........................................................................................... 2

      1.2.1 Current Technology ............................................................................................ 5

   1.2 Motivation .................................................................................................................... 6

2. Energy Dependence of Thermoluminescent Dosimeters in Broad Spectrum X-Ray Beams ......................................................................................................................... 7

   2.1 Introduction ................................................................................................................... 7

   2.2 Materials and Methods .............................................................................................. 8

      2.2.1 X-Ray Irradiator ................................................................................................. 8

      2.2.2 Half Value Layer (HVL) Measurements ................................................................ 9

      2.2.3 HVL Matching ..................................................................................................... 9

      2.2.4 Thermoluminescent Dosimeters (TLDs) ........................................................... 9

      2.2.5 Individual Correction Factor (ICF) Measurements ............................................. 9

      2.2.6 Calibration Curves ............................................................................................. 10

   2.3 Results ......................................................................................................................... 10
List of Tables

Table 1: HVL Measurements for beams with F4 (2.5 mm Al + 0.1 mm Cu) filter ............ 10

Table 2: Uncertainty budget for IC dose measurement .............................................. 15

Table 3: Exposure parameters used from mouse phantom study .............................. 24

Table 4: Table summarizing phantom dose from averaging the dose measured from each TLD used in the exposure ................................................................. 27

Table 5: Mouse phantom doses determined from the nano-FOD detector ................. 28

Table 6: Investigated temperature values ........................................................................ 33

Table 7: Exposure parameters for energy dependence (all exposures with 30 sec length) .................................................................................................................. 36

Table 8: Patient log summary; Patients with mixed energy plans have beam energies listed separately ............................................................ 52

Table 9: Phantom study dose results ................................................................................ 55

Table 10: Summary of acquisition parameters for MDCT A, CTB & CT C ............... 62
List of Figures

Figure 1: Percentage depth dose curves for kilovoltage x-ray beams with energies 50-280 kVp at an SSD of 30 cm [7] .................................................................................................................................................. 3

Figure 2: Exposure plot used to measure HVL at 135 kVp with treatment filter in place. The HVL is taken as exponent or 0.0730 mm Al in this case. ......................................................................................... 11

Figure 3: Calibration curves for batch 3, purchased in 2007, with treatment filter in place ........................................................................................................................................................................ 12

Figure 4: Calibration curves for batch 7, purchased in 2003, with treatment filter in place ........................................................................................................................................................................ 13

Figure 5: Calibration curves for batch 11, purchased in 2011, with treatment filter in place ........................................................................................................................................................................ 13

Figure 6: Scatter plot denoting the calibration curve slope changes with HVL in all three investigated batches .................................................................................................................................................. 14

Figure 7: Y-axis projection of Monte Carlo simulation geometry. A monoenergetic electron beam is directed toward the positive z-axis ........................................................................................................ 21

Figure 8: (a) top-view of the schematic at the central plane with recess provided for TLD placement (b) front view of the plexiglass phantom and stand (not used) ............................................................................. 22

Figure 9: Photon spectrum calculated via Monte Carlo methods. The y-axis denotes the normalized number of photons counted .................................................................................................................. 25

Figure 10: TLD calibration curve used to convert light output to dose .................................................................................................................. 26

Figure 11: Nano-FOD calibration curve for fiber E4 taken at 320 kVp relating dose to water with the integrated detector signal .................................................................................................................................................. 28

Figure 12: Phantom dose comparison from plexiglass mouse phantom irradiation .................................................................................................................. 29

Figure 13: Temperature dependence geometry where the x-ray beam was located directly above the nano-FOD .................................................................................................................................................. 34

Figure 14: Custom made spherical phantom for angular dependence measurements, the 90-degree measurement is shown[37] .................................................................................................................. 35
Figure 15: MV X-Ray calibration geometry ................................................................. 37

Figure 16: Voltage plot showing the variability in raw voltage response with temperature ........................................................................................................................................... 38

Figure 17: Angular dependence results in longitudinal and transverse axes [37, 39]........ 39

Figure 18: Energy dependence data showing the calibration factor CF at kVps ranging from 40 to 320 kVp .................................................................................................................................................. 40

Figure 19: MV x-ray calibration plots for converting integrated response to dose .......... 41

Figure 20: Linearity results showing the linear track of integrated scintillation vs exposure [35] ...................................................................................................................................................... 41

Figure 21: Real time power output over a total of 108 mins ........................................ 42

Figure 22: Side-view of calibration set up with beam entering through top surface .... 49

Figure 23: Beam geometry for phantom study; Nano-FOD placed at location 1 ......... 50

Figure 24: Dose data for all enrolled trial patients ......................................................... 56

Figure 25: Adult male anthropomorphic model 701-D phantom (CIRS, Inc., Norfolk, VA, USA) with MOSFETs inserted for organ dosimetry ........................................................................................................ 61

Figure 26: Effective dose per scan for two level lumbar fusions (Superior FOV) ......... 65

Figure 27: Effective dose per scan for two level lumbar fusion (Inferior FOV) ........... 66

Figure 28: Effective dose per scan for four level lumbar fusions ................................. 66

Figure 29: Dose reduction data for CT B; The bar heights are a ratio of the dose outputs relative to the no reduction setting (100%) ........................................................................................................ 67

Figure 30: Nano-FOD raw voltage signal with dose rate area highlighted ................. 72

Figure 31: Nano-FOD voltage signal with area highlighted for dose measurement of peak three ................................................................................................................................................... 73

Figure 32: Phantom geometry set-up ............................................................................ 74
Figure 33: Mouse profile summary ................................................................. 75
Figure 34: Rat profile summary .................................................................... 76
# List of Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAPM</td>
<td>American Association of Physicists in Medicine</td>
</tr>
<tr>
<td>ADCL</td>
<td>Accredited Dosimetry Calibration Laboratory</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CF</td>
<td>Correction/Calibration Factor</td>
</tr>
<tr>
<td>CPE</td>
<td>Charged Particle Equilibrium</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DUHS</td>
<td>Duke University Health System</td>
</tr>
<tr>
<td>flair</td>
<td>FLUKA Advanced Interface</td>
</tr>
<tr>
<td>FLUKA</td>
<td>Fluktuerende Kaskade</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>HDR</td>
<td>High Dose Rate</td>
</tr>
<tr>
<td>HVL</td>
<td>Half Value Layer</td>
</tr>
<tr>
<td>ICF</td>
<td>Individual Correction Factor</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LLD</td>
<td>Lower Limit of Detection</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>MOSFET</td>
<td>Metal Oxide Semi-Conductor Field Effect Transistor</td>
</tr>
<tr>
<td>Nano-FOD</td>
<td>Nano-Fiber Optic Detector</td>
</tr>
<tr>
<td>OSL</td>
<td>Optically Stimulated Luminescence</td>
</tr>
<tr>
<td>OEM</td>
<td>Original Equipment Manufacturer</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PBC</td>
<td>Pencil Beam Convolution</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computed Tomography</td>
</tr>
<tr>
<td>TG-61</td>
<td>Task Group -61, of AAPM</td>
</tr>
<tr>
<td>TLD</td>
<td>Thermoluminescent Dosimeter</td>
</tr>
<tr>
<td>TPS</td>
<td>Treatment Planning System</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric Modulated Arc Therapy</td>
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</table>
Acknowledgements

To start, I would like to acknowledge my advisor, Dr. Terry Yoshizumi for providing me with much needed guidance and feedback over the course of completing this work. In addition, he has shared a wealth of knowledge in the field of medical health physics as well as invaluable mentorship and advice. Next, I would like to acknowledge my committee members. Dr. Joseph Lo, Dr. Oana Craciunescu, Dr. David Kirsch, and Dr. Rathnayaka Gunasingha for their time and contributions to shaping this project. I would also like to thank the members of the Duke Clinical Research Nurse Coordinator staff, Tykeytra Dale and Carla Blackwell for their assistance in recruiting patients and data acquisition for the clinical trial. To my lab mates in DRDL, I am forever thankful for all you’ve done including data acquisition, brainstorming and every day motivation.
1. Introduction

This dissertation aims to inform researchers on the challenges of dose standardization across institutions and characterize a novel detector for in vivo dosimetry. Overcoming the challenges of reproducibility could improve the landscape of preliminary cancer research by easing the transitions of new researchers who intend to improve upon older results.

1.1 Background

Radiobiologic assays using small animal models are the foundation of most basic cancer research. It has been noted that in some cases, a variance in dose of 10% could alter biological response from 5% to 90% levels. This is due to the extreme steepness in some radiation biology response curves [1]. This response demonstrates the importance of minimizing dose uncertainty in small animal studies [2, 3]. Despite the presence of additional variables in small field radiation dosimetry and the effects of dosimetric inaccuracies on results, small animal dosimetry is typically simplified into a single look-up table. This look-up table determines exposure time to reach a target whole-body dose, typically defined at the mid-point of the animal. Device manufacturers or institutional physics groups usually tabulate these tables. Although these values have been shown to be accurate in water equivalent material, the geometry can vary in actual exposure due to immobilization equipment and target specific dosimetry is not readily
available since tabulated data usually references only a defined whole-body dose in the center of a representative phantom.

Beyond the simplistic approach of using a dose rate table, the calibration methodologies to determine dose rate tables can vary at different institutions. These differences can be attributed to size differences in genetic strains [4] as well as variety in calibration methodologies and dosimeters. In addition to equipment differences, in small volumes, the effects of scatter are magnified [5].

The lack of uniform experimental radiation procedures across the small animal dosimetry explains to a large degree the considerable variation in doses and experimental radiation procedures across the research community. A comprehensive, time-efficient, and translatable approach is needed to achieve harmonization of irradiation and dosimetry procedures used at small animal irradiator laboratories [6].

1.2 Small Animal Dosimetry

Small animal irradiation can be easily performed with commercial x-ray and gamma-ray irradiators. Due to this application, commercial x-ray irradiator units have become common in radiation biology research. X-ray irradiators produce a polyenergetic beam with varying degrees of penetrating power. X-ray beams can be categorized based on the range of energies present, where a “hardened” beam has more penetrating power with a higher effective energy and a “softer” beam has a lower
effective energy and is less penetrating in soft tissues. Irradiators can be further
categorized based on beam quality or maximum output energy. Orthovoltage
irradiators, commonly used for small animals, usually operate in the range of 130-320
kV, producing a “harder” beam[6].

Regardless of the beam quality, the poly-energetic beam produced via an X-ray
generator tube means that the dose deposited in tissue is attenuated as a function of
tissue depth as shown in Figure 1.

![Percentage depth dose data](image)

**Figure 1: Percentage depth dose curves for kilovoltage x-ray beams with energies 50-280 kVp at an SSD of 30 cm [7]**

Much of the dose is deposited at a shallow depth in tissue. Typical dose rates
from these machines are 1 – 3 Gy/min at 50 cm from the source. Actual dose rates vary
based on source-to-subject distance, collimator, beam filtration (hardness) and generator settings.

In addition to the varying attenuation, field sizes vary significantly based on the irradiation goal. At our institution, whole body irradiations are completed inside 20 cm, square fields. However, for target specific irradiations, fields can also be adjusted to small fields, using various sizes of collimators from 3 to 40 mm in a single dimension. Collimating a beam to such small dimension introduces many variables not found in larger fields. The collimator housing adds scattered radiation to the field and changes the dose distribution across the field. Limiting the field size in this manner also affects the effects of the electron backscatter within the field [8].

As institutions and researchers acquire new equipment that is simpler to use, x-ray units are typically operated by users without physics support following initial set-up and training by vendors. However, experiments can have widely varying methods of set-up requiring complex calibration and dosimetry support. This has led to a documented lack of reproducibility in a variety of small animal studies [6, 9, 10]. A primary contributing factor in this is the lack of standardization of dose delivery in small animals.
1.2.1 Current Technology

A wide variety of x-ray dosimeters are currently available. Many of these, such as ion chambers are more suited to larger geometries and typically underestimate true dose to the animal. Commonly used dosimeters include radiochromic film, thermoluminescent dosimeters (TLDs), and optically stimulated luminescence dosimeters (OSLs) are more suited in terms of size for the diminutive size of most mouse and rat models. However, these dosimeters are highly invasive and typically used in vivo for only entrance and exit doses, not a true measure of internal dose, neither organ nor whole body dosage.

Occasionally, TLDs or OSLDs are used in conjunction with tissue equivalent mouse phantoms to determine an estimate of the prospective dose to be delivered in vivo. These simplified models provide some information on the dose intended to be delivered but the effects of tissue inhomogeneity in small animals in largely unknown. The nano-fiber optic detector developed at our institution has the potential to overcome many of these concerns in vivo, real-time x-ray dosimetry since it can be placed inside a mouse, via a catheter, prior to sacrificing the animal to verify delivered dose.

However, the ease of use and wide availability of TLDs leaves them as the primary dosimeter in dose verification surveys across multiple institutions [9].
1.2 Motivation

Small animal dosimetry standards at our institution have been standardized since 2005. Small incremental improvements have been made over the years, such as the recent reintroduction of a plexiglass scatter platform, discussed in Appendix C. However, even with years of expertise and trusted data, our institution had never participated in any sort of outside dose verification study. Identical cylindrical phantoms were irradiated in a self-shielded x-ray irradiator with exposures parameters determined using our standard methodology. Mid-line phantom dosages were measured using in-house calibrated TLDs, as well as a set of micro TLDS, that were calibrated at a different laboratory. Preliminary results showed an approximately 20 percent reduction in delivered dose vs. target dose. Since such data would drastically impact the perceived accuracy of past biological assays and radiobiological studies, an investigated was launched to determine the cause of such a gross error in dose measurements. The results of this early study directly lead to the investigated discussed in chapter 2.
2. Energy Dependence of Thermoluminescent Dosimeters in Broad Spectrum X-Ray Beams

One of the major concerns in multi-institutional studies is a consistent calibration curve. Most commonly used dosimeters have some known energy dependence and very few x-ray irradiators have identical spectra. For one of the most commonly used dosimeters, i.e. TLDs, this chapter investigates the appropriateness of current calibration matching methodologies.

2.1 Introduction

Radiobiology experiments in small animals rely heavily on orthovoltage x-ray irradiators [11]. Since most studies use uniform and relatively homogenous whole-body irradiations, it can be assumed that accurate dosimetry is less important. However, dose relative response curves can be very steep and ±10% variations in dose can lead to a mortality range of 5-90% in mice models [2]. In the realm of small animal dosimetry, the documented lack of reproducibility is more concerning [9, 12]. In such cases, the cost, time and effort dedicated to the study is wasted [13].

The lack of uniform experimental radiation procedures across the small animal dosimetry explains to a large degree the considerable variation in doses and experimental radiation procedures across the research community. A comprehensive, time-efficient, and translatable approach is needed to achieve harmonization of irradiation and dosimetry procedures used at small animal irradiator laboratories [6].
The use of thermoluminescent dosimeters (TLDs) has been accepted as the gold standard in small animal dosimetry. Much of the data on the energy dependence of TLDs has been investigated via MC simulations in narrow energy spectrums based on gamma ray emitters such as Co-60 and Cs-137 [14]. Many small animal irradiators are orthovoltage x-ray machines with x-ray energies ranging from 225 kV to 320 kV. To achieve accurate dosimetry in orthovoltage x-ray machines TLD must be calibrated with irradiator specific parameters such as HVL and kVp setting. The same approach must be employed to achieve reproducible dosimetry among collaborating research centers.

The aims of this study, therefore, are (a) to investigate how TLD-100 dosimeter response is affected by the variety of photon energies produced in typical orthovoltage x-ray irradiators, and (b) to share this knowledge to achieve harmonization in TLD calibration method.

2.2 Materials and Methods

2.2.1 X-Ray Irradiator

All measurements are taken on a self-shielded x-ray irradiator (Precision X-Ray: XRAD320, North Branford, CT). The irradiator provides kVp levels up to 320 kVp and a maximum dose rate of > 15 Gy/min at 320 kVp, 12.5 mA and no beam hardening filters in place.
2.2.2 Half Value Layer (HVL) Measurements

HVL measurements were taken with our treatment filter (2.5 mm Al + 0.1 mm Cu) in place at 5 kVp values: 135, 200, 250, 320 kVp. Additional aluminum filters were placed 20 cm from the ion chamber detector to determine exposure changes. Five filtration levels were measured, and an exponential fit was used to determine the beam HVL.

2.2.3 HVL Matching

To match the HVL values at each kVp, aluminum and copper filter were placed at approximately 20 cm from the shelf surface and HVL measurements were repeated until measured HVL measurements were within ±5% of the HVL measured with the treatment filter in place.

2.2.4 Thermoluminescent Dosimeters (TLDs)

The TLDs used were commercially available TLD-100 chips (LiF, Manufacturer). Initial acceptance testing is done on a per batch basis, which includes uniformity testing where dosimeters whose response is outside 2 standard deviations of the average dosimeter response are rejected. Prior to irradiation, dosimeters were annealed at 400°C for 1 hour followed by 2 hours at 100°C.

2.2.5 Individual Correction Factor (ICF) Measurements

Each batch was exposed to a uniform x-ray field to determine the individual response of each TLD in the batch and order was maintained and updated over all
exposures. Dosimeters were stored for 24 h prior to response readout. An individual correction factor (ICF) was determined by averaging the response for all TLDS in the batch and dividing by the individual TLD’s response with the equation below.

**Equation 1: Equation used to calculate ICF for TLD batches**

\[ ICF = \frac{nC_{avg}}{nC_{ind}} \]

where \( nC_{avg} \) is the batch average response in nC/R to a uniform exposure and \( nC_{ind} \) is the nC/R response of any single TLD in the batch. These ICFs were used in conjunction with the HVL of the beam it was measured in.

### 2.2.6 Calibration Curves

Calibration curves were achieved by exposing a total of 15 TLDs, in groups of 3, to 5 separate dose levels. The levels corresponded to approximately a 10, 6, 4, 2 and 1 cGy exposure. The exposure lengths were maintained across all three batches, but small deviations in dose levels are to be expected due to ramp up time from the x-ray irradiator. The TLD responses were then fit to a linear equation and the slope and intercept values were recorded.

### 2.3 Results

#### 2.3.1 HVL Data

<table>
<thead>
<tr>
<th>kVp</th>
<th>HVL (mm Al)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
All HVLs are tabulated in Table 1. A sample HVL plot is shown below for our 135 kVp treatment beam.

For HVL matching, a single exception was made when matching the 250 kVp beam to the 150 kVp treatment HVL. In this case, the HVL match was 6.1% since it was the lowest measurement possible, i.e. an open beam, at 250 kVp.
2.3.2 ICF Measurements

ICFs were determined at each kVp investigated and found that ICFs ranged from 0.87 to 1.25 in Batch 3, 1.11 to 0.91 in Batch 7, and 1.21 to 0.82 in Batch 11.

2.3.3 Calibration Curves

Calibration curves with the treatment filter (F4; 2.5 mm Al + 0.1 mm Cu) in place for each batch are shown below.

![Batch 3 Calibration](image)

**Figure 3:** Calibration curves for batch 3, purchased in 2007, with treatment filter in place
Figure 4: Calibration curves for batch 7, purchased in 2003, with treatment filter in place

Figure 5: Calibration curves for batch 11, purchased in 2011, with treatment filter in place
2.3.4 HVL/Slope Correlation

The slope from all 21 measured calibration curves was plotted versus the HVL of the measured beam. A linear fit model was applied to each batch and found low $R^2$ values although the slope in each case was very small.

![Slope vs. HVL](image)

**Figure 6:** Scatter plot denoting the calibration curve slope changes with HVL in all three investigated batches.

The coefficient of variation for each batch was determined to be 24.10, 38.33, and 34.73% for batches 3, 7 and 11, respectively.

2.4 Discussion

This study included three batches received at varying time points for two reasons: (1) to assess the variability between batches and (2) to confirm that our results were not limited to errors in a single batch. Our results showed that the dose error
trends were consistent across all three batches. As expected, each batch response was varied in terms of calibration curve slope and kVp groupings.

The trend displayed in Figure 6 is indicative of HVL being an inappropriate match for TLD dosimetry. If the HVL matched the beams appropriately, no large vertical deviation at a single HVL is expected. If the true dose is assumed to be determined using a calibration curve measured in a beam identical to the irradiation beam, doses determine via HVL matched curves lead to a range of dose errors, up to 300% overestimation in some cases. Batch 11 had the lowest average dose error, -2.10%, but there was wide variation in the error percentages, over 30 percentage points. The highest average dose error was in Batch 7 with 49.66% and a standard deviation of 78.52 percent.

Errors in our true dose assumptions are primarily linked to Type B errors from the ion chamber since the dosages were calculated based on the calibration curve equations. The error from the ion chamber which was used to measure both HVL and dosages used in the calibration curves. Type A/Statistical errors are not included in the calibration curves since only one exposure was performed per data point. Error bars are included in the calibration curve plots showing the standard deviation between TLD responses. An uncertainty budget is listed below.

Table 2: Uncertainty budget for IC dose measurement

<table>
<thead>
<tr>
<th>Uncertainty Components</th>
<th>Type B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accredited Dosimetry Calibration Lab (ADCL) Calibration</td>
<td>1.9</td>
</tr>
<tr>
<td>Ion chamber display</td>
<td>0.5</td>
</tr>
<tr>
<td>Time</td>
<td>0.1</td>
</tr>
<tr>
<td>Charge</td>
<td>0.05</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Quadratic Sum</td>
<td>1.97</td>
</tr>
</tbody>
</table>

It has been shown that the energy dependence of TLD-100 dosimeters could be up to $60\pm5\%$ [15]. Our data agrees with this study, though data from Carinou et al was acquired using narrow spectrum beams. In this case, the goal was to compare energy response of two dosimeters, so the energy dependence spectrum was sampled less finely at the range typically used for small animal irradiation.

The American Association of Physicists in Medicine (AAPM) addressed the lack of a machine-specific dosimetry protocol for clinical x-ray beams in Task Group 61 (TG-61) [16]. While this document does include a detailed protocol for reference and relative dosimetry, the protocol was written for clinical radiotherapy machines. This suggests significantly larger scatter mediums than those found in small animal machines. This fact is made obvious considering that the reference dose location for the “in-phantom method” is 2 cm below the phantom surface and typical mouse phantoms are only 2 cm in depth.

Narrow beam x-ray spectra results suggest that low energy photon response in TLD-100 dosimeters requires special attention [14]. The results of this study suggest that HVL alone is not an appropriate method to determine the correct calibration curve to convert from light output to dose. The response curve in broad spectrum x-rays at orthovoltage levels is dependent on both peak energy and mean energy.
An earlier study found TLD energy response curves to be significantly less linear at low energy x-rays when compared to responses from $^{60}$Co rays [17]. However, this data was acquired at 35 keV which is significantly lower than the energies used clinically. This study has improved on these results to show that in the clinical range of 135 and 320 kVp, TLD-100 dosimeter was highly linear, but varied in steepness.

In this study, all doses were attained on a one-inch thick plexiglass platform for consistency. However, the work done in this study did not look at the differences in response found by irradiating the dosimeters in various materials. Scatter from the plexiglass material would amplify the low energy photons in the measurement and these could be amplifying difference in the spectrums. It has also been shown that tradition backscatter factors, such as those suggested in TG-61, cannot fully correct for the dose errors that can be found in small animal dosimetry [5]. However, the setup is indicative of small animal irradiations at our institution.

### 2.5 Conclusions

Matching only HVL between irradiation and calibration beams can lead significant dose errors at true dose levels near 2 Gy. There was less variation between doses at lower energies, such as 135 and 150 kVp. In higher energy beams, there is a larger contribution of photons at characteristic energies. To minimize dose errors, the results of this study lead us to conclude that it is necessary to match both HVL and kVp to achieve an accurate dose calibration curve for TLD-100 chips. This latter requirement
becomes formidable task to achieve when multicenter irradiator laboratories are involved with each laboratory having different irradiators from different manufacturers.
3. Monte Carlo - Mouse Phantom Study

The calibration metric for true dose measurements in Chapter 2 assumes the calibration methodology for TDLs discussed is appropriate. This chapter aims to verify the physical calibration methodology in use at our institution for TLD small animal dosimetry by comparison with Monte Carlo particle transport simulation.

3.1 Introduction

Monte Carlo particle transport simulation is still considered the gold standard in dosimetry applications, especially those where physical dosimetry is difficult to obtain reliably [18-22]. Since TLDs are generally accepted as the gold standard of physical measurements, the most appropriate dose comparisons to be made are with those done via Monte Carlo simulation.

Monte Carlo simulation can provide highly detailed, i.e. high-resolution, dosimetry data in simulations done with high-resolution geometry input. Since the data output is highly dependent on data input, it is very important to ensure that the x-ray generator and phantom data input is as precise as possible. In many cases, information may need to be acquired from an equipment manufacturer to appropriately model x-ray generation in proprietary systems.

With this information, a Monte Carlo model can be used to more efficient gather dosimetric data that can be easily repeated such as in “digital clinical trial data” where multiple data sets are generated from Monte Carlo simulations on patient specific
geometry. In small animal dosimetry specifically, Monte Carlo simulations are being used as the basis for the next generation small animal dose assessment, organ-specific dose prescriptions similar to those done in human radiotherapy [23].

3.2 Materials and Methods

3.2.1 Monte Carlo Simulation

Fluktuierende Kaskade (FLUKA) [24], a fully integrated Monte Carlo simulation package, that has a variety of use cases in medical physics [25]. It has been shown to be a viable tool in patient dosimetry for positron emission tomography (PET) and single photon emission computed tomography (SPECT)-CT applications [26]. In this study, FLUKA advanced interface (flair), was used to model the X-RAD 320 small animal irradiator cabinet. The X-RAD 320 can produce up to 320 kVp beam at a maximum beam current 12.5 mA. For small animal radiotherapy applications, the treatment filter, F4 (2.5 mm Al + 0.1 mm Cu), is often used. The x-ray field size is set at 20 cm x 20 cm with a source-to-shelf distance of 50 cm. The original equipment manufacturer (OEM) shelf which is 3 mm of stainless steel, is used to hold samples and animals during exposures.
Figure 7: Y-axis projection of Monte Carlo simulation geometry. A monoenergetic electron beam is directed toward the positive z-axis.

All Monte Carlo transport codes require geometry and material definitions of the sample that is irradiated. A cylindrical plexiglass phantom used for small animal dosimetry with two LiF TLDs in place was used as our irradiation sample. A schematic of the phantom is included below.
Figure 8: (a) top-view of the schematic at the central plane with recess provided for TLD placement (b) front view of the plexiglass phantom and stand (not used).

The flair program export dose deposited, in Gy, per electron. To convert this data to dose per exposure, as reported from other dosimetry, the equation below is used.

**Equation 2: Equation used to determine dose per exposure from FLUKA output files**

\[
Dose = Dose_{\text{exported}} \times \# \text{ of electrons produced}
\]

where \( Dose_{\text{exported}} \) is the dose per electron from calculated in the output file and \( Dose \) is the dose delivered per exposure. The number of electrons produced is calculated from the beam current and exposure characteristics. The equation that accomplishes this shown below.

**Equation 3: Equation determining the number of electrons emitted per exposure**

\[
\# \text{ of electrons produced} = \frac{A}{q} t
\]
where is the amperage on the x-ray tube, in A, q is the charge of an electron, in C, and t is the exposure time, in s.

A total of $6.25 \times 10^7$ electrons were included in each simulation for a total of 35 cycles.

### 3.2.2 Verification

To verify the finding from our MC calculations, dose data was verified with empirical data acquired from the nano-FOD as well as TLDs. The exposure set up was maintained from the simulation with field size and source to shelf distances maintained. The TLDs were placed in specially designed recessed within the phantom and the nano-FOD was placed a separate phantom. This phantom is identical to the TLD phantom except the recess are not present, instead a 1 mm diameter hole was drilled to the center of the phantom so that the dose measurement points are identical between the two phantoms. Exposure parameters are included in below in Table 3.
Table 3: Exposure parameters used from mouse phantom study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>kVp</td>
<td>320</td>
</tr>
<tr>
<td>mA</td>
<td>10</td>
</tr>
<tr>
<td>Exposure time (s)</td>
<td>150</td>
</tr>
<tr>
<td>Beam Filtration</td>
<td>2.5 mm Al + 0.1 mm Cu</td>
</tr>
</tbody>
</table>

3.2.2.1 TLD Experiment

The TLDs were annealed at 400°C for one hour, then 100°C for two hours prior to exposure and read at least 24 h post-exposure. Dose measurements were determined via calibration curves measured to a NIST-calibrated ion chamber. Three TLDs were irradiated at each calibration point and a total of five calibration points were included. Calibration points were measured at 320 kVp, 10 mA and exposure lengths of 30, 60, 120, 180 and 240s. Each TLDs was corrected for differences in response with a ICF correction factor measured in the manner discussed in previous chapters.

Two calibration TLDs were placed inside the plexiglass TLD phantom per exposure for a total of 6 irradiated dosimeters. Dose data from each TLD was averaged to calculate dose per run for a total of 3 runs.

3.2.2.2 Nano-FOD Experiment

The nano-FOD calibration curve was measured in-air with a NIST-calibrated ion chamber. The calibration was done in air and a linear calibration curve was measured.
with a total of 4 dose points achieved by varying lengths of exposure time (30, 60, 120, 240 s). Voltage signals were integrated over the length of the exposure to create a calibration curve converting integrated signal to dose. Three in-phantom exposures were taken, and the integrated signals were converted to dose per run.

3.3 Results

3.3.1 Monte Carlo Data

The spectrum generated via Monte Carlo calculations is shown below. This is the filtered spectrum generated after bremsstrahlung photons exited the Al and Cu filtration.

![Photon Spectrum](image)

**Figure 9**: Photon spectrum calculated via Monte Carlo methods. The y-axis denotes the normalized number of photons counted.
The spectrum was directed downwards at the model plexiglass phantom atop a one-inch thick plexiglass platform for backscatter. Dose is quoted to the LiF material inside the phantom identical in shape and dimension to TLD dosimeters used in physical measurements. The Monte Carlo simulated dose was 697.5 ± 774.15 cGy.

### 3.3.2 TLD Data

The measured calibration curve for the TLD data is shown below.

![Batch 11 Calibration Curve, 320 kVp, F4 Filter](image)

**Figure 10:** TLD calibration curve used to convert light output to dose

The calibration curve was highly linear as expected. The resulting dose measurements are tabulated below.
Table 4: Table summarizing phantom dose from averaging the dose measured from each TLD used in the exposure

<table>
<thead>
<tr>
<th>Run</th>
<th>Light Output (nC)</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33447.76</td>
<td>501.27</td>
</tr>
<tr>
<td></td>
<td>32306.6</td>
<td>486.33 SD</td>
</tr>
<tr>
<td></td>
<td>Avg 493.80</td>
<td>10.57 SD</td>
</tr>
<tr>
<td>2</td>
<td>36514.72</td>
<td>541.45</td>
</tr>
<tr>
<td></td>
<td>35958.83</td>
<td>534.17 SD</td>
</tr>
<tr>
<td></td>
<td>Avg 537.81</td>
<td>5.15 SD</td>
</tr>
<tr>
<td>3</td>
<td>33635.57</td>
<td>503.73</td>
</tr>
<tr>
<td></td>
<td>42070.44</td>
<td>614.23 SD</td>
</tr>
<tr>
<td></td>
<td>Avg 558.98</td>
<td>78.13 SD</td>
</tr>
<tr>
<td>Avg</td>
<td>530.20</td>
<td>33.25 SD</td>
</tr>
</tbody>
</table>

**Mouse Irradiation Data**

3.3.3 Nano-FOD Data

The measured nano-FOD calibration curve is shown below in Figure 11.
Figure 11: Nano-FOD calibration curve for fiber E4 taken at 320 kVp relating dose to water with the integrated detector signal.

The dose data from the three in-phantom runs is shown below.

Table 5: Mouse phantom doses determined from the nano-FOD detector

<table>
<thead>
<tr>
<th>Run</th>
<th>Signal (V-s)</th>
<th>Dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>718.345</td>
<td>672.78</td>
</tr>
<tr>
<td>2</td>
<td>714.158</td>
<td>668.83</td>
</tr>
<tr>
<td>3</td>
<td>710.950</td>
<td>665.81</td>
</tr>
<tr>
<td>Avg</td>
<td></td>
<td><strong>669.14</strong></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td><strong>3.50</strong></td>
</tr>
</tbody>
</table>

3.4 Discussion

A bar graph summary of doses calculated from all three included methodologies in this chapter is shown below.
Figure 12: Phantom dose comparison from plexiglass mouse phantom irradiation

Larger deviations than expected were shown in the physical TLD exposure data. This is likely due to issues with the machine ramp up time. It may be possible to improve precision in this data by including additional warm-up time, or equipment upgrades. To address these concerns in radiobiological experiments, an accelerated QA schedule is used on the irradiator used for these experiments. The accuracy of the TLD data would be significantly improved by a repeated exposure in a more consistent x-ray generator.

The nano-FOD data is likely the most accurate of the comparison data since it is the only dosimeter capable of same-day calibration and exposure. Measuring in this manner eliminates the machine warm-up variable. In more consistent irradiator environments TLD and nano-FOD dose agreement was found to be within 10%.
Although the percent difference in average dose between nano-FOD and Monte Carlo was small, 4.07%, the SD shown in the Monte Carlo results is significantly higher. The precision of the Monte Carlo data could be significantly improved upon with a larger particle number per simulation and increased simulation cycles. Further improvements on the Monte Carlo experiment such as the elimination of the x-ray generation as well could improve the precision of the measurement. By removing the x-ray generation, the simulation speed can be increased, to do this, the x-ray spectrum must be generated previously and imported into the Monte Carlo program.

3.5 Conclusion

Good agreement with Monte Carlo results further proves that the calibration method discussed in chapter 2 which involves matching both HVL and kVp is appropriate for TLD dosimetry in orthovoltage x-ray fields. The Monte Carlo data needs to be improved upon to reduce the large deviation shown.
4. Performance Characteristics of Novel Nano-Particle Based Detector System

In chapter 1, we discussed some of the pit falls of current detectors in small animal and small field dosimetry. To combat these challenges, our institution developed a novel scintillation-based fiber optic detector with sub millimeter size. This dosimeter has the potential to impact a variety of fields, especially real-time small animal organ dosimetry. This chapter characterizes the detector system in detail as well as a brief overview of current implementation of the detector. All works in this chapter were not completed independently sections on the and lifetime radiation effects included data acquired through a collaborative effort in Duke Radiation Dosimetry Laboratory.

4.1 Introduction

Bulk Yttrium oxide activated with Europium ions, [Y2O3;Eu] has been used as the scintillator material in a wide variety of X-ray computed tomography (CT) detectors [27]. By taking advantage of the increased scintillation of the nanocrystalline form [28], a fiber optic based detector system was developed with the capability to detect radiation on a submillimeter scale in real time.

To allow for real time detection, a fiber optic cable is used. Current fiber optic detectors are typically used in conjunction with plastic scintillators [29] which do offer improvements in tissue-equivalence over inorganic scintillators [30]. However, many of these detectors are one to several mm in a single dimension [31-33].
Our organic scintillator-based fiber optic detector system (nano-FOD) improved resolution to ~0.1 mm [34]. This differentiates our detector from many other dosimeters since it can be used for small field dosimetry as well as in vivo applications. This manuscript intends to generally characterize the current generation of our detector system.

4.2 Materials and Methods

4.2.1 Nano-FOD Detector System

A nano-crystalline inorganic scintillator composed of \((Y_{1.9}O_{3};Eu_{0.1}, Li_{0.16})\) was developed at our institution [35]. This scintillator produces 611 nm optical photons in the presence of ionizing radiation fields. Through radiative recombination, the material releases absorbed photon energy as 611 nm optical photons [36]. A pellet of this material approximately 50 microns in thickness is affixed to the end of 600-micron diameter silica core optical fiber. This fiber optic cable is coupled to a femto-watt sensitive photo diode (Thor Labs PDF10A diode) that samples light output in real-time and displays voltage values on screen via Lab View software. A red filter is placed just before the diode sensor to filter out light generated outside the scintillator. The displayed voltage values are proportional to dose rates and can be transformed to dose or dose rates via calibration curves and integration as needed.
4.2.2 Temperature Dependence

Fiber detectors were affixed to the bottom of a plexiglass water tank. The tank was filled with the water height requirement for the circulating heater. A diagram of the set-up is included below. Detector response was evaluated at 12 points between 2.2 and 50.30 degrees Celsius. The specific values are listed in Table 6.

Table 6: Investigated temperature values

<table>
<thead>
<tr>
<th>Exposure #</th>
<th>Average Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.20 C ± 0.14</td>
</tr>
<tr>
<td>2</td>
<td>5.80 C ± 0</td>
</tr>
<tr>
<td>3</td>
<td>10.25 C ± 0.07</td>
</tr>
<tr>
<td>4</td>
<td>15 C ± 0</td>
</tr>
<tr>
<td>5</td>
<td>19.35 C ± 0.07</td>
</tr>
<tr>
<td>6</td>
<td>23.10 C ± 0</td>
</tr>
<tr>
<td>7</td>
<td>25.90 C ± 0</td>
</tr>
<tr>
<td>8</td>
<td>29.60 C ± 0</td>
</tr>
<tr>
<td>9</td>
<td>36.15 C ± 0.07</td>
</tr>
<tr>
<td>10</td>
<td>42.25 C ± 0.07</td>
</tr>
<tr>
<td>11</td>
<td>46.20 C ± 0.14</td>
</tr>
<tr>
<td>12</td>
<td>50.30 C ± 0.28</td>
</tr>
</tbody>
</table>
Temperature changes were achieved via ice and a circulating water heater. Once the temperature monitor recorded the desired temperature, a 15 min delay allowed the entire water tank to reach equilibrium. Temperature measurements were recorded immediately prior to and following exposure to determine the standard deviation of the water temperature over three exposures and the average temperature was recorded. Once temperature was reached, 3 identical exposures at 100 kVp and 300 mAs were taken. Once integrated over time, the voltage integrals were plotted with temperature to provide an energy dependence curve.

![Diagram](image)

**Figure 13:** Temperature dependence geometry where the x-ray beam was located directly above the nano-FOD

### 4.2.3 Angular Dependence

Previous work determined the angular dependence via the use of 4” diameter spherical phantom shown below.
Figure 14: Custom made spherical phantom for angular dependence measurements, the 90-degree measurement is shown[37]

Identical exposures were taken at 120 kVp at 30-degree increments along the two main detector axes. The calculated deviation between each measurement was used to determine the angular dependence of our detector.

4.2.4 Energy Response

Since our scintillator has an effective Z significantly greater than that of water, \( Z_{\text{eff}} = 39.31 \), some energy dependence is expected. However due to the small dimensions of our scintillator, it is not expected to significantly perturb the measurement field.

4.2.4.1 Orthovoltage X-Rays

At orthovoltage levels (40 kVp – 320 kVp) the detector and an ion chamber were placed at the center of a 20 x 20 cm field. The response of each detector was measured at 20 kVp increments and calculated the ratio of nano-FOD response and dose rate in
water. Appropriate f-factors at each kVp were used to convert exposure values to dose in water. F-factors and exposure parameters are tabulated in Table 7.

### Table 7: Exposure parameters for energy dependence (all exposures with 30 sec length)

<table>
<thead>
<tr>
<th>kVp</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>140</th>
<th>160</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>mA</td>
<td>30</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>f-factor</td>
<td>0.911</td>
<td>0.915</td>
<td>0.919</td>
<td>0.923</td>
<td>0.927</td>
<td>0.928</td>
<td>0.930</td>
<td>0.935</td>
</tr>
</tbody>
</table>

**Table 7: cont.**

<table>
<thead>
<tr>
<th>kVp</th>
<th>200</th>
<th>220</th>
<th>240</th>
<th>260</th>
<th>280</th>
<th>300</th>
<th>320</th>
</tr>
</thead>
<tbody>
<tr>
<td>mA</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>f-factor</td>
<td>0.938</td>
<td>0.940</td>
<td>0.941</td>
<td>0.943</td>
<td>0.944</td>
<td>0.946</td>
<td>0.948</td>
</tr>
</tbody>
</table>

### 4.2.4.2 MV X-Rays

Cerenkov light produced in high energy fields distorted our diode measurements in high energy x-ray fields. To account for this, a dual fiber subtraction method was developed. By exposing identical lengths of fiber, the Cerenkov signal from our dose measurements can be subtracted after correcting for diode sensitivities.

Our final calibration method involves the use of the two-fiber system in a water depth calibration, similar to previously published methodology [38].
In Figure 15, the two nano-FOD fibers are placed at the black dot in the center of the solid water blocks. The 0.5cm of bolus is used to close the air gaps in solid water due to the insertion of the nano-FOD as well as to cushion the detector from the weight of the solid water. Ten centimeters of solid water were used as backscatter. The field size and SSD were set to 10 x 10 cm and 100 cm, respectively and dose values were taken from the machine PDD tables. A total of 5 depths were recorded in each calibration curves for each fiber used: 2.5, 5.5 7.5, 10.5 and 12.5 cm.

4.2.5 Linearity

In published work the detector response in a variety of x-ray spectrums with maximum energies of 40, 80, 120, 220 and 225 keV [9]. To collect this data, a NIST calibrated ion chamber and nano-FOD were placed in a central x-ray field location.
4.2.6 Lifetime Radiation Effects

A prior study using our first-generation system, examined the present of any nano-FODs aging or degradation of sensitivity for cumulative doses. To achieve this, the dosimeter was placed inside a Cs-137 irradiator with a measured dose rate of 15.2 Gy/min.

4.3 Results

4.3.1 Temperature Dependence

Detector response varied no more than ±5% over much of the investigated range. At the most extreme point, a significantly higher response was observed.

Figure 16: Voltage plot showing the variability in raw voltage response with temperature
4.3.2 Angular Dependence

At 120 kVp, angular dependence was shown to be minimal with < 4% change in response. Along the first axis, detector response varied a maximum of 3.8%. Response varied less along the second axis at 2% variation.

![Angular Dependence Graph](image)

Figure 17: Angular dependence results in longitudinal and transverse axes[37, 39]

4.3.3 Energy Response

4.3.3.1 Orthovoltage X-Rays

A peak in energy response at around 80 kVp was observed. Higher correction factor (CF) values show that the detector is more sensitivity near this keV range.
4.3.3.2 MV X-Rays

A linear relationship with dose and depth in MV level x-rays was observed. Steeped slopes in higher energy beams were also noted, as expected with the more significant changes in energy for higher energy beams.
4.3.4 Linearity

By integrating the light output of the nano-FOD, the nano-FOD signal tracked highly linear at all the kVps investigated.
4.3.5 Lifetime Radiation Effects

In 8 runs, the nano-FOD was irradiated for a total of 108 mins which delivered a cumulative dose of 1638.5 Gy. During these exposures, no major shifts in detector sensitivity measured in power output were observed.

Figure 21: Real time power output over a total of 108 mins

4.4 Discussion

The nano-FOD detector has been shown to be a viable detector in a variety of applications. Due to its small size, small animal irradiator geometry lends itself to nano-FOD use. In high dose rate (HDR) brachytherapy using $^{192}$Ir sources, detector sensitivity allowed for dose accuracy with TPS within 20%. There was also no detector saturation in this environment even with 1.5 cm of clinical sources ranging from 5-10 Ci. [40]

In microbeam radiation therapy, the nano-FOD can be used to determine accurate real time dosimetry such as the continuous dose rate at the beam peak as
compared to radiochromic film measurements. The device can also determine the lateral beam shape. [34]

The variability detected in temperature response can likely be attributed to the shrink wrap coating placed around the detector to ensure the scintillator was water tight. As expected, the angular dependence of our detector is minimal. Since the active area of the detector is < 1mm³ the nano-FOD does not fall prey to typical geometric sensitivity concerns. The fiber optic cable does limit the available setup locations due to the limited bend radius available, but when bend radii are maintained angular rotation has little input in our measurements.

The linear exposure response lends itself to very simplistic calibration methodologies. However, it is recommended that the nano-FOD be calibrated in a beam identical to the measurement beam in orthovoltage applications. This accounts for the changes in detector sensitivity in polychromatic beams.

For MV beams, it is important to note that the calibration method discussed is specific to depth in water. To account for exposures in different materials, an electron density ratio shown in equation 3 has been shown to be effective,

**Equation 4: Equation to find calibration distance for nano-FOD MV calibration with heterogenous samples**

\[ d_{cal} = \frac{\rho_{e^{-},X}}{\rho_{e^{-},water}} d_{X} \]

where \( d_{cal} \) is the distance used in calibration, \( d_{X} \) is the distance traveled in medium X, and \( \rho_{e^{-},X} \) and \( \rho_{e^{-},water} \) are the electron densities of medium X and water,
respectively. The changes in detector sensitivity with depth are due to the morphing energy distribution in MV fields, since the average photon energy is different in varying lengths of tissue. [41]

The current detector system is capable of measuring dose rates as low as 0.4 mGy/s in x-ray fields. However, this value is highly dependent on the energy and spectrum of the field. So far, a true lower limit of detection (LLD) has not been determined. This is due to the complex relationship between dose and energy dependence of our detector. The relationship between energy and LLD will be explored in future publications.

The lack of signal degradation after over 1600 Gy delivered, means the nano-FOD detector system has the potential for a more permanent installation. With our system, there is the possibility to measure real time exposure rates over an indefinite length of time. The drawback to this is that our current system has a very small active area making it less appropriate for application in area monitoring.

With a generational hardware update to include fiber bundles or light guides to increase the sensitive area of the detector, current applications can be expanded. Future work is also considering the possibility of 3-D chip-based detector volume that could be used as a primitive imaging set-up. The nano-FOD system has potential applications in various rising fields such as neutron and nuclear medicine radiation
therapy beta dosimetry such as I-131 and Lu-177 as well as alpha dosimetry such as As-211.

4.5 Conclusion

The nano-FOD detector system is a highly capable detection device that can achieve ±5% level accuracy in various radiation fields. Its small size and unique calibration methodologies allows for submillimeter detection in a variety of applications.

The energy response of our nano-detector in MV level x-ray fields was evaluated in detail during this chapter. This was accomplished via an IRB-approved clinical trial to be discussed in this chapter.

5.1 Introduction

Our institution developed a sub-millimeter radiation detector based on the novel scintillation properties of a proprietary nano-compound of [$\text{YtO:Li}$]$_{35}$ [35]. Our preliminary investigations lead to several clinical research projects focused on developing new application for the device. Initial investigations in orthovoltage x-rays for small animal studies led to development of a standard operation procedure in gynecological HDR brachytherapy procedures with Ir-192 gamma rays [42]. To expand on these applications, this study aimed to investigate detector performance with high energy X-ray sources.

External beam radiation therapy treats a variety of malignancies with MV energy x-ray beams generated in linear accelerators [43-45]. Treatment methodologies are consistently improving with a variety of dose delivery options such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). These therapies utilize quickly adjusting fields that can be collimated to 1 mm in a single dimension. In addition to field size changes, the varying collimation also leads to
varying dose rates during treatment. All currently available dosimeters are post hoc and hold no record of the changes in dose rate over the course of treatment.

The nano-FOD is a scintillator-based detector that is coupled to a fiber optic cable which transmits light signals to a photodiode in real time. This allows each beam’s dose rates to be visualized over the course of treatment.

The Duke University Health System (DUHS) Institutional Review Board (IRB) for Clinical Investigation approved a clinical trial to determine the feasibility of the nano-FOD in external beam radiation therapy, a high energy x-ray environment for dose measurement. Our proposal was designed to monitor skin dose based on the simplicity in dosimeter placement thus minimizing the burden on patients and staff during accrual.

In addition to simplifying patient accrual, measuring skin dose allowed us to measure detector performance in a variety of therapy types and geometries. Skin dose was not a limiting factor in the radiation therapy treatments investigated, since it skin complications can lead to sensitivities that would limit detector placement. However, it provides a readily available value that can be compared to the value displayed in the treatment planning software (TPS).
5.2 Materials and Methods

5.2.1 Nano-FOD Detector

Our nano-particle detector system includes three components: (1) a micron sized pressed pellet of the nano-crystalline material, (2) a fiber optic cable to transmit the scintillation light and (3) a femto-watt sensitive photodiode detector that samples light output in real-time and records proportional voltage values.

5.2.2 Nano-FOD Cerenkov Correction

In high energy fields, the Cerenkov light, generated in the fiber optic cable, overwhelmed the scintillator signal. To ensure all recorded light is scintillator emissions, a red filter is placed just prior to the photo diode for collection. Our setup was improved to include an additional “blank” fiber for signal correction. The additional fiber was connected to a separate photo-diode and appropriate corrections were made to account for sensitivity differences in the two diodes.

5.2.3 Nano-FOD Calibration

The nano-FOD was calibrated to depth in water to account for any variations in beam energy during tissue attenuation. Output was determined at 5 depths (2.5, 5.5, 7.5, 10.5, and 12.5 cm) in solid water with a 0.5 cm layer of bolus to protect the device and seal any air gaps and 10 cm of back scatter. With a 10 x 10 cm field size and standard 100 cm source to surface distance, dose was determined using measured beam tables for the treatment machine. A schematic of the calibration set-up is shown in Figure 22.
Nano-FOD output curves were determined for three photon treatment energies (6, 10, and 15 MV) and fitted to a linear curve. To use the calibrations, depths traveled in the body were measured from the center of the beam face to either the device marker or the vertical axis directly below the device marker. Distances for each beam were used to convert the voltage integrals to dose measurements.
5.2.4 Phantom Study

Our calibration methodology was tested by delivering a 7-beam, 6 MV photon beam IMRT prostate treatment to an anthropomorphic Rando® phantom and measuring skin dose with our dosimeter through a single fraction. The total fraction dose to the target volume was set at 2 Gy. The measured dose was then compared to the calculated dose given by the TPS at the same location. Figure 23 shows the beam geometry for the phantom treatment.

Figure 23: Beam geometry for phantom study; Nano-FOD placed at location 1
5.2.5 Patient Accrual

Our IRB approved clinical trial enrolled our first patient in January of 2016, enrolling patients with a variety of malignancies for skin dose measurements. A total of 59 fractions completed on 13 patients are included in this report. A summary of enrolled patients and disease sites are included in Table 8. The nano-fiber optic detector (nano-FOD) was placed directly on patient skin, below bolus if used, inside a disposable cover and secured with paper tape.
Table 8: Patient log summary; Patients with mixed energy plans have beam energies listed separately

<table>
<thead>
<tr>
<th>Patient</th>
<th># of Fractions</th>
<th>Treatment Type</th>
<th># of Beams</th>
<th>Beam Energy (MV)</th>
<th>Disease Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surf-01</td>
<td>5</td>
<td>IMRT (Static-I)</td>
<td>9</td>
<td>10</td>
<td>Vulvar</td>
</tr>
<tr>
<td>Surf-02</td>
<td>4</td>
<td>IMRT (Static-I)</td>
<td>9</td>
<td>10 (6)/6 (3)</td>
<td>Abdomen</td>
</tr>
<tr>
<td>Surf-04</td>
<td>3</td>
<td>IMRT (Static-I)</td>
<td>4</td>
<td>6 (2)/15 (2)</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-06</td>
<td>3</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-07 w/Bolus</td>
<td>2</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-07 w/o Bolus</td>
<td>3</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-08 w/Bolus</td>
<td>1</td>
<td>IMRT (Static-I)</td>
<td>4</td>
<td>6 (2)/15 (2)</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-08 w/o Bolus</td>
<td>3</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-09</td>
<td>5</td>
<td>VMAT</td>
<td>3</td>
<td>10</td>
<td>Endometrial</td>
</tr>
<tr>
<td>Surf-10</td>
<td>5</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-11 w/Bolus</td>
<td>2</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>15</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-11 w/o Bolus</td>
<td>3</td>
<td>IMRT (Static-I)</td>
<td>4</td>
<td>6 (2)/15 (2)</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-12 w/Bolus</td>
<td>3</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-12 w/o Bolus</td>
<td>2</td>
<td>IMRT (Static-I)</td>
<td>2</td>
<td>6</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-13</td>
<td>5</td>
<td>IMRT (Static-I)</td>
<td>11</td>
<td>10</td>
<td>Vulvar</td>
</tr>
<tr>
<td>Surf-14</td>
<td>5</td>
<td>IMRT (Static-I)</td>
<td>4</td>
<td>6 (2)/15 (2)</td>
<td>Breast</td>
</tr>
<tr>
<td>Surf-15</td>
<td>5</td>
<td>IMRT (Static-I)</td>
<td>16</td>
<td>6 (4)/10 (12)</td>
<td>Anal</td>
</tr>
</tbody>
</table>
5.2.6 Dose Delivery

Treatments were delivered according to our institution’s standard of care and patients were not selected via treatment types. An additional CT marker was placed during simulation that corresponded to a planning marker denoting the location of the nano-FOD. The treatment planning software (TPS) dose was measured by recording the calculated dose in skin directly below the visible marker on the brightest slice location.

5.2.7 Nano-FOD Dose Measurements

The nano-FOD system displays voltage values that are proportional to dose rate over time. To calculate dose, the voltage values were first integrated over the exposure time for each beam. Since the calibration was done to depth in water, the distance traveled by the beam prior to encountering the detector was required. In cases where the beam axis does not lie in the same plane as the nano-FOD, the distance travelled to the plane directly below the nano-FOD was measured. The measured distances were corrected radiological depths for any beams passing through bone via equation 4 [46],

**Equation 5: Equation to determine radiological depth**

\[ d_r = d_{ST} + \frac{\rho_{e,\text{bone}}}{\rho_{e,\text{water}}} d_{bone} \]

where \( d_r \) is the distance used to determine the correction factor, \( d_{ST} \) is the distance travelled in soft tissue, \( d_{bone} \) is the distance traveled in bone, \( \rho_{e,\text{bone}} \) and \( \rho_{e,\text{water}} \) are the electron densities of bone and water, respectively. This distance was then
compared to the calibration charts to find a correction factor that is appropriate to calculate dose via equation 5,

**Equation 6: Equation to determine dose per beam in MV patient acquisition**

\[ D_{\text{beam}} = CF \times VI \]

where \( D_{\text{beam}} \) is the dose in cGy to soft tissue from a single beam, \( CF \) is the correction factor in cGy/V-s found on the calibration chart and \( VI \) is the integrated voltage value in V-s for the beam. Doses from each beam were summed to find the dose per fraction.

**5.3 Results**

**5.3.1 Phantom Study**

The RANDO® phantom delivery let to a percent difference in dose of 3.01%. The raw difference in dose per beam was less than 1 cGy or less than 6% of the total dose delivered during the treatment. The results are summarized in Table 9.
Table 9: Phantom study dose results

<table>
<thead>
<tr>
<th>Beam</th>
<th>Total Depth (cm)</th>
<th>Bone Depth (cm)</th>
<th>Radiological Depth</th>
<th>CF (V-s / cGy)</th>
<th>Dose (TPS)</th>
<th>Dose (Nano-FOD)</th>
<th>% diff Dose (cGy)</th>
<th>Raw Diff (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21.1</td>
<td>4</td>
<td>24.2</td>
<td>0.055</td>
<td>13.00</td>
<td>13.15</td>
<td>1.18%</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>15.5</td>
<td>0</td>
<td>15.5</td>
<td>0.050</td>
<td>0.80</td>
<td>0.63</td>
<td>-21.79%</td>
<td>-0.17</td>
</tr>
<tr>
<td>3</td>
<td>11.5</td>
<td>0</td>
<td>11.5</td>
<td>0.047</td>
<td>0.40</td>
<td>0.99</td>
<td>146.54%</td>
<td>0.59</td>
</tr>
<tr>
<td>4</td>
<td>8.8</td>
<td>0</td>
<td>8.8</td>
<td>0.046</td>
<td>1.40</td>
<td>1.72</td>
<td>22.56%</td>
<td>0.32</td>
</tr>
<tr>
<td>5</td>
<td>8.7</td>
<td>0</td>
<td>8.7</td>
<td>0.045</td>
<td>1.60</td>
<td>1.26</td>
<td>-21.33%</td>
<td>-0.34</td>
</tr>
<tr>
<td>6</td>
<td>11.5</td>
<td>0</td>
<td>11.5</td>
<td>0.047</td>
<td>0.40</td>
<td>0.77</td>
<td>92.88%</td>
<td>0.37</td>
</tr>
<tr>
<td>7</td>
<td>15.5</td>
<td>0</td>
<td>15.5</td>
<td>0.050</td>
<td>0.60</td>
<td>0.24</td>
<td>-60.63%</td>
<td>-0.36</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>18.2</strong></td>
<td><strong>18.75</strong></td>
<td><strong>3.01%</strong></td>
<td><strong>0.55</strong></td>
<td></td>
</tr>
</tbody>
</table>

5.3.2 Clinical Trial

The total average percent difference, determined by measuring the percent difference in total dose for all patients between the nano-FOD and TPS, was 10.32 ± 0.13%. The full study results are included in Figure 24. In the figure, the TPS bar represents the TPS dose per fraction and the Nano-FOD bar is the average dose per fraction measured by the nano-FOD. Each point on the bar is the individual fraction dose measured by the nano-FOD for each included fraction.
5.4 Discussion

All TPS dose measurements were achieved via anisotropic analytical algorithm (AAA) implemented in Varian Eclipse system. It is known that all model-based dose calculations are limited inside the build-up region near the surface where charged particle equilibrium (CPE) has not yet been established. However, studies have shown the AAA is more accurate than previous calculation algorithms such as pencil beam convolution (PBC) and PENELOPE [47-49].

The phantom study was designed to include multiple beams and a relatively complicated IMRT treatment plan. By selecting a nano-FOD location that was only in the direct path of a single beam, all the assumptions posited in the calibration development were proved. The single beam in the path of the dosimeter included some bone requiring the radiological depth adjustment. Since the overall dose agreement to the TPS was within 5%, the calibration methodology was accepted as appropriate. Positive
results in the phantom study led us to push forward and pursue a clinical trial with our detector.

The clinical trial included a wide variety of patients with several different malignancies and treatment sites. The treatment strategies included intensity modulate radiation therapy (IMRT) and volumetric modulated arc radiotherapy (VMAT) both of which involve high flux variation during treatment. It was found that the nano-FOD was unaffected by the varying dose rates and provided real-time visual feedback to the dose rate changes.

From the clinical trial, improvement in dose accuracies by including bolus were observed. This was especially apparent in patients such as Surf-12 whose treatment involved beams with mixed energies. Bolus is used to boost skin surface dose and in patients where bolus was used, our dose accuracy benefitted from the additional effects of a more uniform dose distribution over the treatment area.

The primary limitation of our study was the variability in detector placement between fractions due to human errors. Markers placed on patient skin can fade over time; and each day the tape used to secure the detector could be placed slightly different due to issues such as clothing or patient skin sensitivities. Our calibration is depth-dependent and assumes the detector location is identical to that of the marker placed during the planning CT. This assumption leads to additional dose errors being introduced to the nano-FOD measurement.
The TPS algorithm has some potential to inaccurately calculate skin dose based on the body contours placed within the patient treatment plan. Some studies have shown that the TPS has the potential to underestimate skin doses by up to 14% when compared to Monte Carlo simulated doses [50]. Empirical data suggests that radiochromic film measurements can lead to both over and underestimation of skin dose ranging from 69.3% to -23.1% [51]. Data shown in this study shows a slight reduction in dose variance to between 1.83% and -52.24%. There is potential to improve this data using different TPS dose calculation algorithms and improvement techniques discussed in literature [50]. These methodologies will only improve the accuracy of the TPS, not the calibration methodology for the nano-FOD.

5.5 Conclusions

Our study has demonstrated the feasibility of nano-FOD usage for skin dosimetry usage in MV x-ray radiation therapy. With appropriate calibration and Cerenkov filtration, clinically acceptable dose accuracy of around 10% can be achieved.
Appendix A: Patient Dose Comparison for Intraoperative Imaging Devices Used in Orthopedic Lumbar Spinal Surgery

A.1 Background and Significance

A rise in the American obesity rate has led to increased numbers of spinal complications requiring surgical intervention [52, 53]. The advancement of spinal surgery in recent years has led to increased reliance on intraoperative imaging. With renewed demand, imaging technology has broadened to include a variety of different types such as serial radiography, C-arm fluoroscopy, and 3-dimensional imaging. Such technology is typically marketed directly to orthopedic surgeons. In doing so, imaging protocols are often provided directly from the manufacturer. These settings are rarely optimized for specific use cases such as spinal surgery.

Since most devices are calibrated to provide diagnostic quality images, the radiation dose is likely higher than needed for surgical applications. Bone-soft tissue contrast is easy to achieve, and the spine is one of the largest organs in the body so exceptional image quality is not needed. Personnel radiation exposure has been shown to be increased in spinal surgery specifically when compared to other orthopedic specialties [54]. From this, we can infer that patient dose is also increased in this sub-specialty of orthopedics, but we are unaware of any published data on patient dose in spinal surgery.
Our institution has the distinctive availability of several intraoperative imaging systems from which to select including MDCT scanner A, two mobile CT units – CT B & CT C, C-arm D, and Fluoro E. Although a number of studies have reported on the radiation exposure of some of the modalities [54-56], and just recently Hecht et al published on the accuracy of instrumentation using CT B [57], we are unaware of any literature examining radiation exposure of MDCT A or CT B. Additionally, we are unaware of any study that has directly compared all these modalities with respect to commonly performed spinal surgery. This information is essential for any surgeon to accurately assess which intraoperative imaging modality best fits his or her risk/benefit profile.

Therefore, the aim of this study was to determine and compare the amount of radiation exposure to patients during a two level (three vertebral bodies) and four level (five vertebral body) lumbar fusion using one of five imaging systems available at a single institution.

**A.2 Materials and Methods**

**A.2.1 CIRS Phantom**

We utilized an adult male anthropomorphic phantom (Model 701-D, CIRS, Inc, Norfolk, VA, USA) for patient radiation exposure. The phantom is designed to model a 160-pound male (72.6 kg) with a height of 5 foot 8 inches (1.73 m). The calculated body mass index (BMI) of the phantom is 23.0 which is considered within the normal range.
(18.5-24.9) [58]. Two layers of adipose equivalent material were progressively added to increase the BMI of the phantom to 28 (179 lbs.) and 31 (198 lbs.), placing the phantom within overweight and obese ranges, respectively. The phantom was placed prone on a carbon fiber OR table for all data acquisition. Figure 25 provides a representative image of phantom position.

Figure 25: Adult male anthropomorphic model 701-D phantom (CIRS, Inc., Norfolk, VA, USA) with MOSFETs inserted for organ dosimetry

A.2.2 MOSFET Calibration

High-sensitivity metal oxide semiconductor field effect transistor (MOSFET) detectors (Hi Sensitivity model 1002RD, Best Medical Canada, Ottawa, Canada) were calibrated in air with each scanner in a stationary vertical beam position based on previously established calibration methods.
C-Arm D and Fluoro E automatically modulate tube potential and beam current based on patient thickness. By placing the phantom in the beam, we determined an average tube potential to calibrate the MOSFET dosimeters.

### A.2.3 CT Scan Parameters

Scan parameters were determined using patient protocols. MDCT A used beam current modulation based on an initial topogram image taken before each image series acquisition. CT B modulated beam current based on inputted patient weight. Image acquisition parameters for MDCT A, CT B and CT C are summarized in Table 10.

**Table 10: Summary of acquisition parameters for MDCT A, CTB & CT C**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDCT A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube Potential (kVp)</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Beam Current (mAs)</td>
<td>150</td>
<td>308</td>
<td>632</td>
</tr>
<tr>
<td><strong>CT B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube Potential (kVp)</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Beam Current (mAs)</td>
<td>110</td>
<td>127.6</td>
<td>141</td>
</tr>
<tr>
<td><strong>CT C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube Potential (kVp)</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Beam Current (mAs)</td>
<td>128</td>
<td>320</td>
<td>400</td>
</tr>
</tbody>
</table>

Fields of view were determined based on the procedure. In two level fusions, two fields of view could be used: superior field of view which captured lumbar
vertebral levels 1-3 (L1-3) and the inferior field of view which captured lumbar vertebral levels 3-5 (L3-5). Four level fusions require visualizing all 5 lumbar vertebrae.

**A.2.4 Organ Dosimetry**

Skin entrance exposure was measured using a 0.18 cc ion chamber (Model 10x5-0.18, RadCal Corp., Monrovia, CA) with an electrometer (Model 9015, RadCal Corp.). Placement was adjusted per scan to ensure the dosimeter was consistently within the field of view (FOV).

Twenty high sensitivity dosimeters connected to four readers (Model TN-RD-16, Best Medical Canada) connected through a mobile MOSFET wireless system (TN-RD-70-W20, Best Medical Canada) were used in data acquisition. MOSFET dosimeters were placed in 12 organ locations corresponding to: liver, spleen, active bone marrow in the thoracic spine, pancreas, kidneys, gall bladder, stomach, colon, active bone marrow in the lumbar spine, pelvis, and sacrum.

**A.2.5 Effective Dose**

Effective dose was calculated using the following equation:

\[
ED \ (mSv) = \sum PVCF_T \times W_T \times PD_T
\]

where PVCFT represents the partial volume correction factor, WT is the tissue weighting factor, and PDT is the point dose for each organ as determined...
experimentally. The partial volume correction factor was based upon an estimation of the irradiated percentage of each organ volume.

All data was summarized using descriptive statistics. Data analysis was calculated using Microsoft Excel (ver. 2010 & 2013, Microsoft Corp., Redmond, WA).

**A.2.6 Dose Reduction**

The manufacturer of CT B offers several reduction modes, and we tested the dose reduction of 3 modes with a central ion chamber measuring machine output. The ion chamber measurement in the dose reduction modes was compared to the unadjusted dose output for an identical patient. We compared the measured exposure reduction to the manufacturer quoted reduction.

**A.3 Results**

**A.3.1 Effective Dose**

Preliminary data showed that the dose output for Fluoro E were below the MOSFET measurement threshold. Since we were unable to acquire consistent point dose measurements, organ doses were acquired from PCXMC (STUK, Helsinki, Finland), a Monte Carlo based patient dose modeling software, using measured beam quality factors.
The effective doses are shown in Figures 26-28. All doses are reported per scan. In cases where the machine was unable to cover all five lumbar vertebral bodies in a single field of view, five level fusion data is reported as the dose sum of the superior and inferior fields of view.

![Two Level (Superior) Lumbar Fusion Diagram]

**Figure 26: Effective dose per scan for two level lumbar fusions (Superior FOV)**
Figure 27: Effective dose per scan for two level lumbar fusion (Inferior FOV)

Figure 28: Effective dose per scan for four level lumbar fusions
For the larger machines where full coverage was feasible, three measurements were taken: superior FOV, inferior FOV and full FOV. It is important to note that in this case, the inferior and superior views are not summed to calculate the full FOV dose. Full FOV dose was determined through a separate helical scan that included all five vertebral levels and due to overhanging effects, may not be equivalent to the summed dose.

### A.3.2 Dose Reduction

The manufacturer stated reduction was found to be within ±1% of the measured reductions. The dose reduction data is shown in Figure 29.

![Dose Reduction Comparison for CT B](image)

**Figure 29:** Dose reduction data for CT B; The bar heights are a ratio of the dose outputs relative to the no reduction setting (100%)

### A.4 Discussion

As expected, we found dose to be on average $30 \pm 3\%$ higher in four level fusion studies than two level fusion studies across all patient sizes. We also noted a decrease in
percent difference between the superior and inferior FOV with increasing patient weight. This is likely due to the increased waist size created by the additional adipose layers. We also noted that the dose trends across patient weight were identical for all five machines in both two and four level fusions.

With increasing patient weight, we expect patient dose to increase as well and in the case of MDCT A and C-Arm D, we found this to be the case. However, CT B demonstrated a decrease in patient dose with increasing patient weight. We attributed this finding to the fact that CT B was unable to adequately adjust output for above average sized patients. CT C and Fluoro E show a peak dose in overweight patients which informs us that the machine was appropriately adjusting to the increase in weight from normal to overweight, but the machine was likely at maximum output for the obese patient.

In addition, dose from the single standard MDCT scanner investigated was substantially higher than that of any other machines. Across all three patients the average difference was 154 ± 16%. In this case since dose in significantly higher, we can assume that the image quality metrics calibrated in this machine are likely well beyond what’s needed in surgical applications and; substantial dose reduction could be achieved with optimized protocols. Our study did not investigate image quality.

In a normal patient with our largest FOV, effective dose ranged from 0.34 to 13.52 mSv per scan. As patient size increased the dose range across the machines
continued to widen. The manufacturer’s dose reduction settings are appropriately adjusting CT B’s output to reduce dose. Although we did not repeat the internal organ measurements, we can infer from the reduction in machine output that the effective doses would adjust accordingly. Using CT B in 50% dose reduction, reduces the dose variation in a three-level fusion for normal patients from 6.16 mSv per scan to 2.91 mSv per scan a 53% reduction. The reduction in obese and overweight patients is lower, 40 % and 37 %, respectively, but still a meaningful reduction especially in cases requiring large numbers of scans. However, widespread implementation of these protocols would require a measure of image quality to ensure the clinical outcome are unaffected by the lower quality images.

A direct comparison of radiation exposure using our five intraoperative imaging systems has not been previously reported in the literature. We endeavored to compare the radiation exposure to patients during a two level and four level lumbar fusion. By focusing on the effective dose measurement, we were able to combine the large number of organ doses we measured into a single metric of comparison for all five machines. However, our effective dose calculation was limited by the fact that we did not measure point dose in all organs. Previous studies verified our partial volume correction factor method with Monte Carlo modeling software[59].

In addition, we acknowledge that our anthropomorphic phantom cannot truly model the heterogeneity of the human body or the breadth of variation in the patient
cohort receiving spinal surgery. The addition of additional layers of soft tissue approximated increasing obesity but certainly does not represent the heterogeneity of patient body habitus. We also acknowledge that our phantom could only model patients up to the borderline classification of obesity, in significantly overweight patients, the dose trends may not hold. Our phantom model is sufficient in this use case, i.e. dose output comparisons.

A.5 Conclusion

Our work has demonstrated a wide range of patient doses from different imaging systems used for an identical purpose. This observation is highly concerning since patient outcome should be independent of equipment choice. This study provides surgeons with comparative data with respect to radiation exposure for five different imaging systems in order help them make educated decisions regarding the risks and benefits of utilization. Further study of spinal imaging modalities is needed, and future endeavors may include comparative analyses of image quality or experimenting with lower radiation dose settings available with some systems. Importantly, continued efforts are also needed to inform more surgical teams to utilize the physics support in their institution when purchasing imaging systems.
Appendix B: Standard Operating Procedures

B.1 Nano-FOD Voltage Acquisition

Note: The electronics in the nano-FOD dosimeter are radiation sensitive and it is imperative that they be shielded from all radiation sources. In addition, the fiber tips are light-sensitive, and they should be shielded from as much room light as possible. The additional light will increase background and could be find in high flux environments, but very dark backgrounds are required for high sensitivity measurements.

The nano-FOD detector system output is always in V. The calibration methodologies and assumptions vary between applications.

B.2 MATLAB Code

There are two main MATLAB codes used for nano-FOD analysis. The first titled NanoFOD_Calibration_Analysis.m, located inside the Nano-FOD Analysis folder in the Radiation Safety Research Data Bin, calculates 2 major values: integrated signal and time stamps. The code requires an unmodified .xlsx input from the LabView software since the variable names correlate to the specific header names. It will also ask for the sampling frequency and number of samples (Recommended values: 50 Hz, 25 samples).

Note: This file can only be used for the LabView software that accepts 2 inputs only. For LabView taken with up to 5 inputs, please use the MultiplexAnalysis.m file.

The second MATLAB code is titled Brachy_Analysis_V3.m. This code calculates dose from Ir-192 gamma ray sources in high dose rate (HDR) brachytherapy using a
distance-based calibration from AAPM TG-51 formulism. The two variables in output have columns equal to the number of needles used in treatment plus one. The last column is the total dose or a sum of dose from all needles. The code requires the sampling frequency, number of samples, an unmodified .xlsx file and the source activity in Ci at the time of treatment.

Note: Lines 95 and 96 must be updated to measured calibration curve values prior to analysis.

A detailed method of how to use each of these codes is included in the tutorial power point (Nano-FOD Analysis Tutorial 9-30-16_v2.ppt).

**B.2 X-Ray Analysis**

For x-ray calibrations the voltage values are proportional to dose rate. When analyzing data, it is important to determine which data is required from the nano-FOD, i.e. dose vs. dose rate. Dose rate calibrations are acquired by average a portion of peak raw voltage signal highlighted. An example area is shown in the image below.

![Figure 30: Nano-FOD raw voltage signal with dose rate area highlighted](Image)
To go directly from nano-FOD signal to dose, the voltage signal must be integrated. This integration is done by **summing** the integrated voltage signal over the course of the measurement in an area as shown below.

![Nano-FOD voltage signal with area highlighted for dose measurement of peak three](image)

**Figure 31:** Nano-FOD voltage signal with area highlighted for dose measurement of peak three

Integrated voltage is calculated via the MATLAB code. Currently, x-ray dose and dose rate analysis done by hand via Microsoft Excel ®.

### B.3 Gamma Ray Analysis

Current gamma ray applications in HDR brachytherapy assume that the voltage values displayed from the nano-FOD are **proportional to distance from the source**. This is very different from the x-ray assumptions and as such requires specific calibration to Monte Carlo simulated dosages based on source-to-detector distances. Due to this, all dose analysis is handled via the MATLAB software code.
Appendix C: Duke Small Animal Irradiation Dose Tables

C.1 Motivation

In previous years, Duke Radiation Dosimetry Lab recommended whole body irradiations with the addition of a plexiglass platform beneath animal subjects. Over time, the platform was removed from our protocols. We aimed to determine whether the recommendation was appropriate.

C.2 Mouse Backscatter Summary

Mouse phantoms used in this experiment had a diameter of 2 cm and were placed centrally inside a plexiglass immobilization box. The box was irradiated with and without the addition of a 1 in thick plexiglass platform that was 20 cm, square. Calibrated radiochromic film was sandwiched between two slices of the phantom to acquire a profile along the sagittal plane. A diagram of the setup is shown below.

![Diagram of phantom setup]

Figure 32: Phantom geometry set-up

In each geometry, the phantom was irradiated 3 times for the same exposure length. Normalizing the dose to prescribed central dose showed that 64.41 percent of the...
mouse received at least 95% of the prescribed dose without the plexiglass platform. The platform improved dose coverage in the sagittal plane to 72.58%.

Figure 33: Mouse profile summary

**C.3 Rat Backscatter Summary**

Rat phantoms with a diameter of 3 cm were irradiated identically to that of the mouse set-up. Three film exposures were averaged to provide the profiles shown below.
Figure 34: Rat profile summary

C.4 Small Animal Dosimetry Standard Operating Procedure

For Physicists:

Quality Assurance Testing

Yearly QA reports will be on file with Dr. Terry Yoshizumi for all irradiators.

Dose Rate Tables

Yearly dose rate tables will be compiled for all common geometries. These tables will be compiled for the two main filters in use: F1 and F4. Dose measurements should be completed with either MOSFET or TLD dosimeters and exposures should be at least 1 min in length.

Custom made dose rate tables will be tabulated upon request and documented centrally for future studies.
For Biologists:

*Dose Rate Tables*

Geometries will be clearly labeled in the binder placed at each irradiator. It is important that you locate the appropriate filter prior to exposure. Locate the appropriate filter, geometry, and size and use the included dose rate to calculate exposure length to delivered desired whole-body dose.

If the dose rate tables do not include your desired set-up, i.e. customized shielding, or immobilization devices, please contact Giao Nguyen for a specialized consult.

Note: These tables should be updated after Feb 1st of each year. Please contact Dr. Terry Yoshizumi (terry.yoshizumi@duke.edu) and Giao Nguyen (giao.nguyen@duke.edu) for updated tables.

**C.5 Dose Rate Tables**

**C.5.1 Mouse Models**

C.5.1.1 Applicability

- Data is applicable only to small mice (~2cm in diameter)
- For different geometry, see contacts.

Caution:

- Check to ensure proper filter type in irradiator before Irradiation
Geometry 1.
Table 1.

<table>
<thead>
<tr>
<th>Filter Type</th>
<th>Dose Rate (Gy min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4: 0.1mmCu + 2.5mmAl Filtration</td>
<td>2.871 ± 0.04786</td>
</tr>
</tbody>
</table>

C.5.1.2 Sample Calculation – Exposure Time

MOUSE Phantom X-ray Dosimetry

Location: GSRB II

Experiment Date: 09-02-17

Present: BM, GN

NOTE:

Formula – Exposure Time:

\[
Time (\text{minutes}) = \frac{Dose \text{ Prescribed (Gy)}}{Irradiator \text{ Dose Rate (Gy/min)}}
\]

Sample Calculation

Exposure time needed to irradiate 10Gy:

\[
Time = \frac{10\text{Gy}}{0.7889\text{Gy/min}} = 12.68\text{min}
\]
C.5.2 Rat Models

C.5.1.1 Applicability

- Data is applicable only to rats or large mice (~3cm in diameter)
- For different geometry, see contacts.

Caution:

- Check to ensure proper filter type in irradiator before Irradiation
Geometry 1.

![Diagram of Radiation Source and Phantoms](image)

- **43.58 cm**
- **50 cm**
- **2.54 cm**
- **3 cm**

- **Plexiglass Holder**
- **Rat Phantom**
- **Backscatter Platform**
Table 1.

<table>
<thead>
<tr>
<th>Filter Type</th>
<th>Dose Rate (Gy min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4: 0.1mmCu + 2.5mmAl</td>
<td>2.856 ± 0.04761</td>
</tr>
<tr>
<td>Filtration</td>
<td></td>
</tr>
</tbody>
</table>

C.5.1.2 Sample Calculation – Exposure Time

RAT Phantom X-ray Dosimetry

Location: GSRB II

Experiment Date: 09-02-17

Present: BM, GN

NOTE:

Formula – Exposure Time:

\[
Time \ (\text{minutes}) = \frac{Dose \ Prescribed \ (Gy)}{Irradiator \ Dose \ Rate \ (Gy/\text{min})}
\]

Sample Calculation

Exposure time needed to irradiate 10Gy:

\[
Time = \frac{10\text{Gy}}{0.7889 \text{Gy/min}} = 12.68\text{min}
\]
Bibliography


37. Wang, C., Radiation Dose Estimation for Pediatric Patients Undergoing Cardiac Catherization, in Duke Dissertation, D. University, Editor. 2015.


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Biography

Bria Mudiwa Moore was born on January 9, 1993 in Jackson, MS. In 2009, she began her undergraduate education at Tuskegee University in Tuskegee, AL to obtain a degree in Physics. She graduated summa cum laude in May of 2012 with a Bachelor of Science degree in Physics. She was honored during her time there to serve as a NASA Student Ambassador.

In August of 2012, she entered the Duke University Medical Physics graduate program at Duke University. During her time spent there, she received many awards including a Duke University Chancellor's and Dean's Graduate Fellowship, and a Duke Graduate Student Training Enhancement Grant. She was also awarded 2nd place in the 2016 NC Health Physics society paper competition and the prestigious Robert. Gardener Memorial Fellowship from the National Health Physics Society. She was able to publish papers in several journals including the American Journal of Roentgenology, Medical Physics and Radiology.

Peer Reviewed Publications
