Statistical Evaluation of Alanine Dosimeter Response for Linac and CyberKnife Photon Beams

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1. Introduction

Alanine dosimetry using electron paramagnetic resonance (EPR) spectroscopy is a well-established method for measuring absorbed dose through quantification of radiation-induced free radicals. The alanine/EPR system exhibits excellent linearity, long-term stability, and tissue equivalence in high-dose radiation environments, and is recommended as a reference dosimetry system in ISO/ASTM 51607 and IAEA TECDOC-1188 [1,2]. In addition, alanine dosimeters have been reported to demonstrate high linearity and reproducibility under photon beam irradiation conditions [3].

Although 6 MV photon beams are nominally identical, differences in beam generation mechanisms, irradiation geometry, and collimation systems between linear accelerators (Linac) and CyberKnife platforms may influence detector response characteristics [4]. Distinguishing whether observed slope differences arise from random measurement variability or systematic beam-quality dependence is particularly important for clinical quality assurance (QA). Even small differences in detector sensitivity may lead to systematic dose deviations when calibration curves are transferred between machines. Therefore, rigorous statistical evaluation is required to determine whether the observed differences are statistically significant and clinically meaningful.

In this study, the dose–response characteristics of alanine dosimeters were compared for Linac 6 MV, Linac 10 MV, and CyberKnife 6 MV photon beams. Differences in sensitivity were evaluated using analysis of covariance (ANCOVA). A linear mixed-effects model (LMM) was applied to account for repeated measurements and to estimate slope uncertainty. Furthermore, equivalence testing (TOST) was performed to assess interchangeability among beam modalities within predefined clinical acceptance margins (±3% and ±5%) [5].

2. Methods and Results

2.1 Alanine Dosimeter and Irradiation Conditions

Alanine pellet dosimeters (E2044562, Bruker BioSpin, Germany) were used in this study. Each pellet had a diameter of 5 mm, a height of 3 mm, and a nominal mass of 64.5 mg. The composition consisted of 80% L-α-alanine and 20% polyethylene to ensure structural stability and uniform density.

Photon beam irradiations were performed using a clinical linear accelerator, Elekta Infinity (Elekta AB, Stockholm, Sweden), delivering 6 MV and 10 MV photon beams. The absorbed dose to water was used as the reference dosimetric quantity. Irradiations were conducted under reference calibration conditions at a source-to-surface distance (SSD) of 100 cm and a measurement depth of 5 cm in a water-equivalent phantom.

CyberKnife irradiations were performed using a CyberKnife G4 system (Accuray Inc., Sunnyvale, CA, USA) with a 6 MV photon beam. The irradiation geometry was set at an SSD of 80 cm and a depth of 1.5 cm using a fixed circular collimator (6 cm cone).

Absorbed doses of 1, 5, 10, 15, and 20 Gy were delivered to evaluate linearity over the clinically relevant dose range. At each dose level, four independent alanine dosimeters were irradiated per dose point, allowing assessment of repeatability and enabling subsequent mixed-effects statistical analysis.

Following irradiation, EPR measurements were performed using the peak-to-peak (PtP) amplitude as the dosimetric response parameter. All measurements were conducted under identical spectrometer settings to ensure consistency across beam modalities.

2.2 Linearity Assessment

The dose–response relationship was modeled using linear regression:

$$S = \beta_0 + \beta_1 D$$

Here, S represents the EPR peak-to-peak signal, D denotes the absorbed dose (Gy), β_0 is the intercept, and β_1 represents the dose sensitivity (slope). In the present dataset, all three machines demonstrated excellent linearity (with $R^2 \approx 0.999$ for each machine). Therefore, subsequent comparisons among machines were primarily focused on differences in slope.

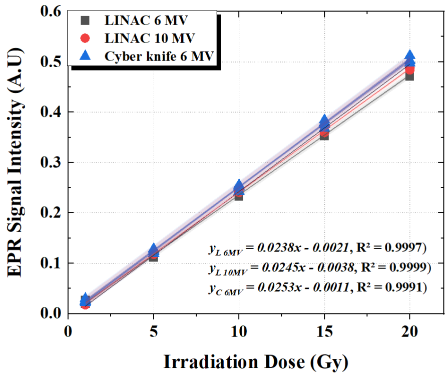

Figure 1. Dose–response curves of alanine dosimeters for Linac 6 MV, Linac 10 MV, and CyberKnife 6 MV photon beams.

2.3 Comparison of Dose–Response Curves Among Machines

Simultaneously compare the dose–response curves among machines, an analysis of covariance (ANCOVA) model including the machine factor (M) was applied:

$$S = \beta_0 + \beta_1 D + \beta_2 M + \beta_3 (D \times M) + \varepsilon$$

where M represents the machine factor (categorical variable), D×M denotes the dose–machine interaction term corresponding to differences in slope among machines, and ε is the error term.

When Linac 10 MV was set as the reference category, the interaction terms were statistically significant for both Linac 6 MV ($p = 0.00899$) and CyberKnife 6 MV ($p = 0.00106$), indicating significant differences in dose sensitivity compared to the reference beam.

2.4 Linear Mixed-Effects Model (LMM)

To account for repeated pellet measurements ($n = 4$ per dose level), a linear mixed-effects model (LMM) was applied:

$$S_{ijk} = \beta_0 + \beta_1 D_i + \beta_2 M_j + \beta_3 (D_i \times M_j) + u_{ij} + \varepsilon_{ijk}$$

Where S_{ijk} represents the signal measured at the i-th dose, j-th machine, and k-th repetition, u_{ij} denotes the random effect at the machine–dose level, and ε_{ijk} represents the residual error associated with repeated measurements. Figure 2 shows the slopes estimated from the linear mixed-effects model accounting for repeated pellet measurements ($n = 4$ per dose). The slopes were 0.023858 for Linac 6 MV, 0.024476 for Linac 10 MV, and 0.025264 for CyberKnife 6 MV, with identical standard errors (SE = 0.001239) across machines. The 95% confidence intervals were narrow and partially overlapping, indicating precise slope estimation with comparable variability among machines. CyberKnife 6 MV exhibited the highest dose sensitivity, suggesting a systematic difference in detector response compared to the Linac beams.

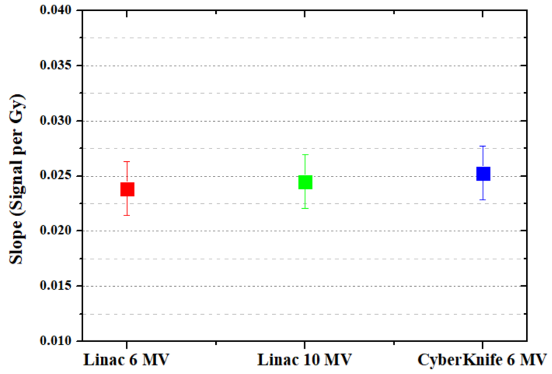

Figure 2. Estimated slopes with 95% confidence intervals for each photon beam modality.

2.5 2.5 Equivalence Testing (TOST)

The slope ratio between machines was defined as $R = \beta_{1,A} / \beta_{1,B}$. Equivalence was determined by whether the 90% confidence interval of R was fully contained within the predefined margins of ±3% or ±5%.

The slope ratio of Linac 6 MV relative to Linac 10 MV was 0.971, satisfying the ±5% criterion. In contrast, the slope ratio of CyberKnife 6 MV relative to Linac 6 MV was 1.062, exceeding the ±5% margin.

Applying the Linac 6 MV calibration to CyberKnife 6 MV would result in an approximate systematic dose bias of +5.9%.

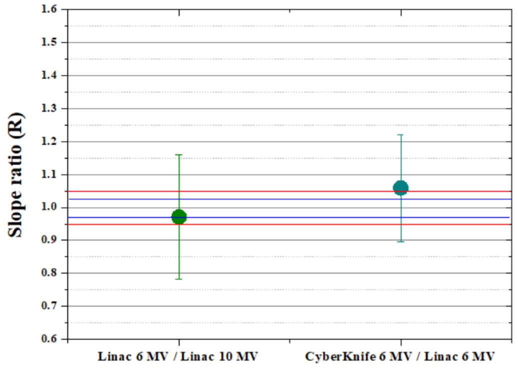

Figure 3. Slope ratios with 90% confidence intervals and equivalence margins (±3% and ±5%).

3. Conclusions

Alanine dosimeter response was statistically evaluated for Linac 6 MV, Linac 10 MV, and CyberKnife 6 MV photon beams. All modalities showed excellent linearity. ANCOVA confirmed significant slope differences. Equivalence testing showed that Linac 6 MV and 10 MV were equivalent under ±5%, while CyberKnife 6 MV exhibited higher sensitivity and did not meet the ±5% criterion.

These findings indicate that machine-specific calibration may be required when applying alanine dosimetry to CyberKnife photon beams. The results also demonstrate the importance of rigorous statistical evaluation to ensure clinical accuracy in beam quality assurance applications.

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