Incorporation of experimental uncertainties associated with *in vitro* determination of radiobiological parameters used in cervical cancer brachytherapy

B. CHOW [1], **B. WARKENTIN** [1], **F. HUANG** [1], **A.M. GAMPER** [1], **G. MENON** [1]

1 Department of Oncology, University of Alberta, Edmonton, AB, Canada

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INTRODUCTION

- Brachytherapy (BT) for locally advanced cervical cancer is prescribed using radiobiological dose
  - Conversion of physical dose to radiobiological (RB) dose requires use of α/β ratio and half-time of repair ($T_{1/2}$)
- Parameter values are uncertain:
  - Conventional assumptions (tumours): α/β: 10 Gy, $T_{1/2}$: 1.5 hr
  - Wide range of literature values: α/β: 6-21 Gy, $T_{1/2}$: 0.15-5.7 hr (Ref 1)
- BT can use high-dose-rate (HDR) or pulsed-dose-rate (PDR) modality
  - **Variance in parameter values** affects assumed equivalency between HDR and PDR treatment schedules
- Our *in vitro* experiments with cervical cancer cell lines using BT treatment regimens established smaller α/β (4.71-6.63 Gy) and larger $T_{1/2}$ (1.6-3.9 hr) values
- This work **identifies the experimental uncertainties** associated with these *in vitro* experiments, and determines their effect on the RB parameter values and corresponding calculations of prescription dose

PURPOSE

To determine and quantify the uncertainties associated with the experimental determination of radiobiological parameters, and their impact on cervical cancer BT dose prescription.

METHOD

- Clonogenic assays were performed using 3 cervical squamous cell carcinoma cell lines: CaSki, C-33 A, and SiHa
- Radiation was delivered in single acute fractions (HDR) or multiple hourly fractions (PDR) using clinical BT afterloaders
  - Experimental setup for a PDR irradiation is shown in Figure 1
- RB parameter values were estimated using least chi-squared method to fit experimental results to the modified linear-quadratic (LQ) model

Uncertainty quantification

- Sources of uncertainty include:
  - Dose delivered: source/plate alignment, source calibration, transit time, effects of material heterogeneities
  - Measurement of cell survival: uniformity of cell distribution, colony counting, variance in experimental conditions
- Uncertainties were determined using multiple methods, as shown in Tables 1 and 2

Impact of uncertainties on dose

- RB parameter values were re-estimated with inclusion of uncertainties
- Two BT boost treatment schedules that give equivalent RB dose when using conventional RB parameters were considered:
  - PDR: 0.73 Gy x 58 pulses
  - HDR: 7.75 Gy/fr x 4 fractions
  - Total dose with external beam radiotherapy (EBRT; 45 Gy in 25 fr) and either BT boost: ~90 Gy EQD2
- EQD2 doses were recalculated over the range of experimental RB values including uncertainties to highlight the potential impact on the assumed equivalency of clinical BT boosts

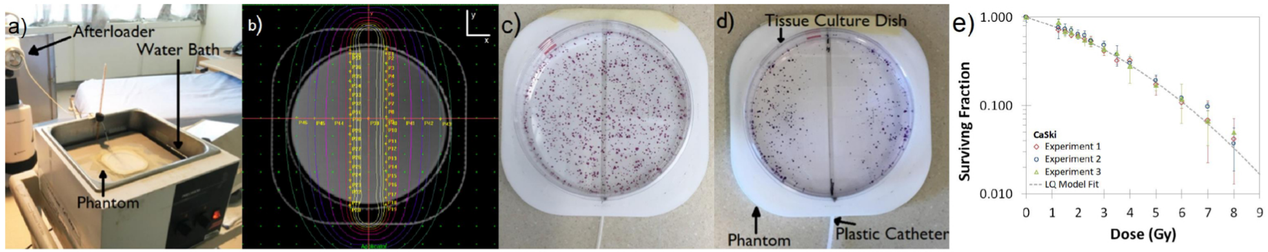

Figure 1: (a) Setup for PDR delivery showing the water bath and a phantom in which a tissue culture dish was placed for irradiation. During HDR delivery, the water bath was not utilized (comparatively shorter irradiation times). (b) CT scan of the phantom with a tissue culture dish inserted and the isodose lines of a planned treatment. 10 cm tissue culture dishes showing cell colonies (stained purple): (c) used as control (0 Gy exposure) and (d) surviving a 5 Gy irradiation prescribed to points ±1 cm from the central catheter. (e) Experimental results from PDR irradiation of CaSki cells, fitted using the minimum least-chi square method to the modified LQ model.

RESULTS

Uncertainty quantification

Table 1: Summary of potential sources of dose uncertainty

Uncertainty Type	Method of Estimation	Uncertainty
Source position: x-axis	Change in dose after shifting source positions by up to 2 mm in Oncentra Brachy	±0.13%
Source position: y-axis		±0.10%
Rotation of dish	Change in dose after shifting source positions 1° around P39 (Figure 1(b)) in Oncentra Brachy	±0.08%
Source strength	Calibration measurement	±1%
Transit time	Ref 2	+0.50% (HDR) +0.74% (PDR)
Effect of heterogeneity	Comparison of dose using TG-43 and Advanced Collapsed Cone Engine (ACE) in Oncentra Brachy	±0.5%
Total uncertainty (Dose)		**±1.24% (HDR) ±1.36% (PDR)**

- Largest potential source of uncertainty for dose delivery is the source strength
- Minimal impact from positional uncertainty of the tissue culture plate

Table 2: Summary of potential source of cell survival uncertainty

Uncertainty Type	Method of Estimation	Uncertainty
Number of cells seeded	Experiments were performed to measure the impact of uncertainty on cell survival rate	Not detected (within statistical noise)
Cells cooling during radiation		
Time between seeding and radiation		
Uniformity of cell distribution	Recounting previous experiments	±3%
Number of colonies identified		±0.76%
Total uncertainty (Survival)		**±3.09%**

- Uniformity of cell distribution was the largest potential source of uncertainty
- Variance in experimental conditions (e.g. time between seeding and radiation) did not significantly contribute to uncertainty
  - Impact of the variance could not be distinguished from counting uncertainty
- Identified uncertainties generally smaller than counting uncertainty
  - Shown in Figure 2, as the majority of survival error remains counting uncertainty

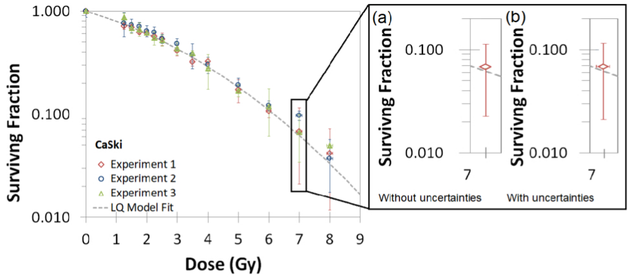

Figure 2: Experimental results from PDR irradiation of CaSki cells, fitted using the minimum least-chi square method to the LQ model with consideration of all identified uncertainties. The 7 Gy data point for Experiment 1 is shown in the inset, with error bars including (a) only counting uncertainty, as shown in Figure 1(e), and (b) counting uncertainty and additional uncertainties determined in both dose (Table 1) and cell survival (Table 2).

Table 3: RB parameters (mean [min – max]) for the 3 cell lines with and without inclusion of uncertainties.

Cell Line		α/β (Gy)	$T_{1/2}$ (hr)
	Conventional values	10	1.5
CaSki	Without uncertainties	5.01 [4.50 - 6.38]	4.05 [2.95 - 4.98]
	With uncertainties	5.01 [4.23 - 6.49]	4.05 [2.78 - 5.13]
C-33 A	Without uncertainties	6.48 [6.10 - 7.21]	1.53 [1.37 - 1.82]
	With uncertainties	6.48 [5.80 - 8.03]	1.53 [1.28 - 1.85]
SiHa	Without uncertainties	5.08 [3.73 - 5.05]	2.40 [2.06 - 2.91]
	With uncertainties	5.08 [3.64 - 7.60]	2.40 [2.01 - 2.92]

- RB parameter range with and without inclusion of uncertainties is comparable
  - Does not impact previous trends: a smaller α/β and larger $T_{1/2}$ than conventionally assumed were still identified

Incorporation of uncertainty on dose

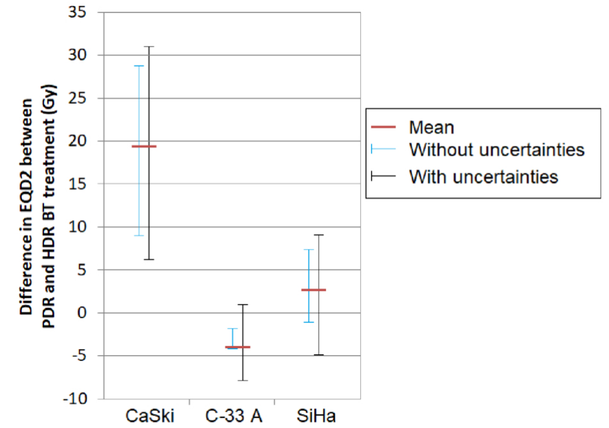

Figure 3: Difference in EQD2 between sample radiation schedules using the parameter ranges determined for each cell line (Table 3). The central line represents the difference using the mean value for each cell line, while the blue and black error bars represent the differences corresponding to the potential ranges in the RB values, without and with full accounting of uncertainties.

- CaSki cells would experience **significantly higher dose from clinical PDR BT**

CONCLUSIONS

- Total effect of uncertainties identified: <1.5% dose uncertainty and <4% cell survival uncertainty
- Range of reported parameters with uncertainties are **similar to those** without inclusion of the uncertainties
- **PDR BT may deliver more radiobiological dose** than conventional HDR equivalent
  - Up to **30 Gy EQD2**
  - Potentially impacts patient outcome

ACKNOWLEDGEMENTS

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REFERENCES

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[2] Menon *et al. Phys Med Biol* 2008;53:3447-3462.

CONTACT INFORMATION

Email: bkchow@ualberta.ca