Large Scale Comparison of In Vitro and Clinical α/β Estimates for Breast, Prostate and H&N Cancer

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ABSTRACT

This study determined, for three common cancers, if in vitro α/β estimates agree with clinical values, and if there are common patterns of discrepancy. Clinical and in vitro estimates of α/β for prostate, breast, and head and neck cancer were examined. Statistical tests were performed to determine a pattern between clinical and experimental values. Monte Carlo sampling was used to determine the underlying distribution of α values for clinical and in vitro. The Poisson TCP model was applied to determine the potential differences between clinical and experimental α/β. Prostate cancer gave median clinical and in vitro estimates of 3.8 Gy and 1.7 Gy respectively. For breast cancer, clinical and in vitro estimates were 3.9 Gy and 3.6 Gy. Head and neck clinical and in vitro were 9 Gy and 14 Gy. Significant correlation was only found with α/β and organ type. TCP curves for in vitro and clinical estimates demonstrated significant differences in estimated tumor control. No conclusive evidence was found supporting an agreement between in vitro and in vivo α/β, though both supported estimates either much lower than the commonly applied 10 Gy, or in the case of H&N cancer, at least 10 Gy. Significant differences existed between in vitro and clinical estimates, and therefore in vitro estimates of α/β cannot directly predict clinical radiosensitivity estimates.

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INTRODUCTION

Radiation therapy schedules are guided by biological models that predict tissue response to dose fractionations, most commonly the linear-quadratic model, which uses the α/β ratio to characterize radiosensitivity. α/β values have been derived from in vitro experiments and clinical outcome data, but the extent to which laboratory estimates reflect clinical behavior remains uncertain. While it has been argued that in vitro measurements reliably predict in clinical responses, evidence has been mixed, with studies reporting both correlations and quantitative differences[1,2]. Nevertheless, many clinically accepted α/β values originated from in vitro work, including the conventional estimate of 10 Gy for most tumors. Clinical studies have suggested lower α/β values for breast and prostate cancer[2,3], while evidence for other tumor types remains limited. Given the difficulty of obtaining reliable clinical estimates, it is important to determine if in vitro α/β values can be translated to clinical practice. This study compares published in vitro and clinical α/β estimates for breast, prostate, and head and neck cancers to evaluate the relationship between preclinical and clinical radiosensitivity estimates.

METHODS AND MATERIALS

A systematic literature review was performed, collecting a total of 141 in vitro and 116 clinical α/β estimates for prostate, breast, and head and neck cancers, spanning 108 studies. Additional variables, including radiation energy, dose rate, cancer stage, adjuvant therapies, and organ site for head and neck cancers, were recorded when available. Correlation analyses was used to evaluate relationships between α/β values and experimental or clinical variables. Differences between in vitro and clinical distributions were assessed using the nonparametric Mann-Whitney U test, while bootstrap resampling (10,000 iterations) was performed to estimate 95% confidence intervals for both α/β and α distributions. Monte Carlo sampling combined with a Poisson tumor control probability (TCP) model was used to generate composite TCP curves from bootstrapped α and α/β distributions, assuming 2 Gy fractions and an initial tumor clonogen population of approximately 1×10^8 cells. Poisson model followed the form

$$TCP = N_0 e^{-\alpha D\left(1+\frac{d}{\alpha/\beta}\right)}$$

Where N_0 is the intital clonogen number, and d and D are the fractional and total dose, respectively.

Table 1. Number of α/β values analyzed in this study.

	In Vitro	Clinical
Prostate Cancer	43	78
Breast Cancer	55	11
H&N Cancer	43	27
Total	**141**	**116**

Table 2. Summary statistics for α/β distributions of all 3 cancer types.

	Prostate Cancer		Breast Cancer		H&N Cancer	
	In Vitro	Clinical	In Vitro	Clinical	In Vitro	Clinical
Mean (Gy)	4.26	2.51	5.32	3.56	10.91	15.41
Median (Gy)	3.76	2.29	3.86	3.60	9.0	14.0
Std Deviation (Gy)	2.35	1.47	4.71	0.70	8.08	8.23
Mann-Whitney U Test: p-value	<0.0001		0.72		0.02	

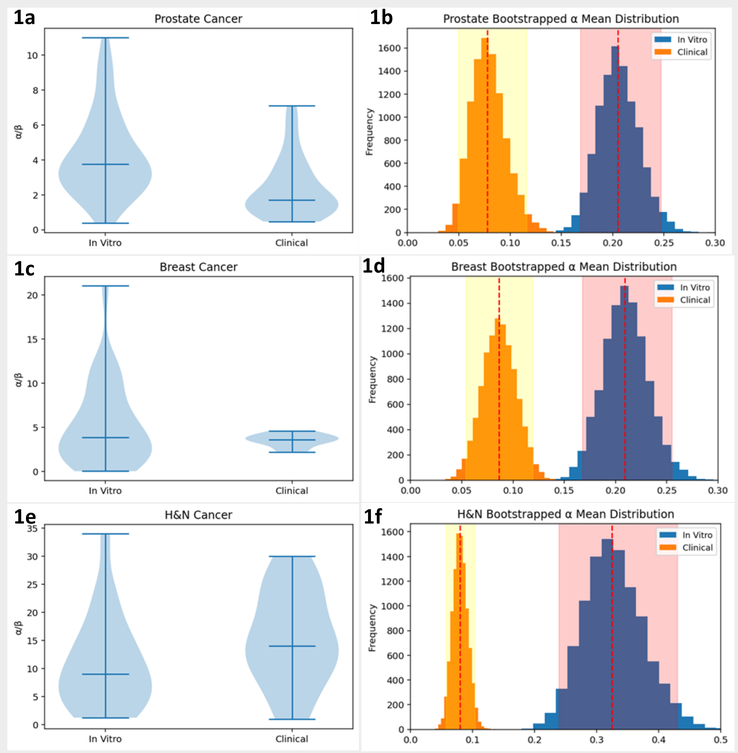
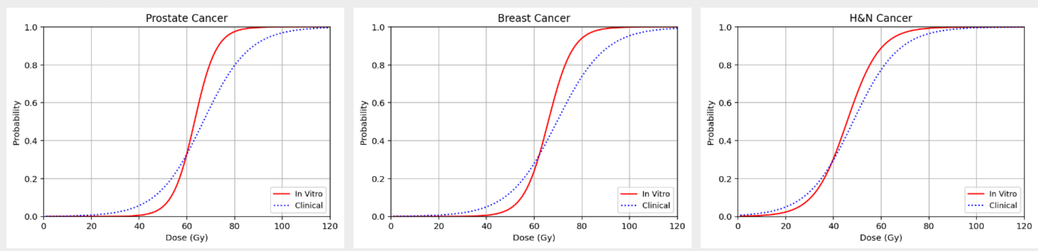


Figure 1. (a,c,e) Violin plots showing the distribution of α/β values of in vitro and clinical data for the three cancer types, with the end caps representing the maximum and minimum values, and the middle line representing the median value. (b,d,f) Sampled distributions of the mean α value for the three cancer types. The vertical red lines represent the median value and the light red and yellow shaded regions represent the 95% confidence intervals.

Table 3. Correlation coefficients for in vitro estimates of α/β with dose rate and photon energy. Correlation coefficients for clinical estimates with adjuvant therapy and cancer stage. In the case of H&N cancer for both estimates, organ type was also evaluated.

	In Vitro			Clinical		
	Dose Rate	Energy	Organ	Adjuvant Therapy	Cancer Stage	Organ
Prostate α/β	-0.224	-0.106	N/A	0.177	0.000	N/A
Breast α/β	-0.143	-0.341	N/A	0.000	0.000	N/A
H&N α/β	-0.046	-0.275	0.506	0.000	0.340	0.481

Figure 2. TCP curves for (a) breast cancer, (b) prostate cancer, and (c) head and neck cancer. The solid red curves represent the in vitro estimates. The dotted blue lines represent the clinical estimates.



RESULTS

Prostate cancer exhibited higher in vitro α/β values than clinical estimates, with median values of 3.8 Gy and 2.3 Gy, respectively, while breast cancer showed similar median values between in vitro (3.6 Gy) and clinical (3.9 Gy) datasets. In contrast, head and neck cancers demonstrated higher clinical α/β values (14.0 Gy) than in vitro estimates (9.0 Gy). Mann-Whitney U testing indicated statistically significant differences between in vitro and clinical distributions for prostate ($P < 0.0001$) and head and neck cancers ($P = 0.02$), whereas breast cancer showed no significant difference, likely because of the smaller clinical sample size. Correlation analyses found no meaningful relationships between α/β values and radiation energy, dose rate, cancer stage, or adjuvant therapy, with organ type being the only variable significantly associated with α/β values in head and neck cancers. Bootstrap analysis further demonstrated that clinical α values were consistently lower than in vitro estimates across all three cancer types. Monte Carlo simulations and Poisson tumor control probability (TCP) modeling revealed substantial differences between TCP curves generated from in vitro and clinical radiosensitivity estimates, particularly for prostate and breast cancers, indicating that laboratory-derived parameters alone do not accurately reproduce expected clinical tumor control.

CONCLUSIONS

The study demonstrates statistically significant differences between in vitro and clinical estimates, in contrast to long-held beliefs these values could be directly applied clinically. Specifically, the α parameter was found to be much larger for in vitro estimates. This suggests that in vitro and clinical α values may be at least correlated, and in vitro values could inform clinical estimates with certain corrections. There are still many cancers that assume an α/β of 10 Gy, without reliable clinical estimates to corroborate that. This study shows that in vitro measurements specific to those cancers can reevaluate those assumptions and, with corrections, could potentially be correlated to clinical values. Despite some prominent claims, no evidence was found to support a direct agreement between in vitro and in vivo α/β estimates.

REFERENCES

1. L.R. Kelland, K.S. Tonkin, G.G. Steel. A comparison of the in vivo and in vitro radiation response of three human cervix carcinomas Radiother Oncol, 16 (1989), pp. 55-63
2. J.C. David, D.S. Robert, J. Kristofer, Z.W. Jian Comparison of in vitro and in vivo α/β ratios for prostate cancer Phys Med Biol, 49 (2004), pp. 4477-4491
3. J. Yarnold, A. Ashton, J. Bliss, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: Long-term results of a randomised trial Radiother Oncol, 75 (2005), pp. 9-17