The impact of dose deviations arising within the dosimetry chain on clinical outcomes

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Purpose

Delivered radiotherapy dose may be compared between clinics due to the traceability of dose to Primary Standards Laboratories (PSL). Uncertainties arise at each point in the calibration chain and thus the actual delivered dose can deviate from that desired.

These uncertainties were quantified for each step:

- calibration transfer to a secondary standard instrument
- transfer to field instruments
- subsequent QA measurement tolerances

Radiobiological modelling was used to predict the clinical impact of these uncertainties for individuals and populations of patients.

The variation in delivered dose due to the dosimetric chain has been put into perspective by comparing with dose ranges in 3D conformal and IMRT techniques.

Methods

Linear-Quadratic (LQ) and Lyman-Kutcher-Burman (LKB) models were implemented to model the effect of systematic and random deviations in delivered dose.
- Individual patients were modelled and aggregated to provide population estimates.

Clinical cases: - Prostate (10yr bPFS and grade 2 rectal bleeding [1])
- Head and neck (2yr survival and xerostomia induction [2])
See Table 1 for further details.

Model Simulations: - Fixed systematic dose shift throughout treatment
- Variation in dose arising due to machine assignment

The variation in dose between plans derived using either 3D conformal or IMRT techniques was quantified based on the plans used within the PARSPORT trial [2].

Dosimetric parameters for the target volume were calculated for and the standard deviation for each determined for each technique. This variation has been compared to that arising from the dosimetry chain.

Results

Linac calibration uncertainty: Uncertainty in the initial transfer of the calibration from PSL to the clinic was determined from on-site audits performed by the National Physical Laboratory (NPL) over 2 decades and is normally distributed with a SD of 0.7% [3]. Uncertainty reduced over time, from 0.8% to 0.4% between 1995 and 2015 respectively.

Beam output uncertainty: Data from over 24,000 multi-centre beam output measurements was used as a basis of the uncertainty following calibration and had a 0.7% SD [4] due to output drift. Daily fluctuations were 0.2% SD.

Summary of uncertainties (SD):		
	Linac calibration (overall mean)	0.7%
	Output variation due to drift	0.7%
	Daily fluctuations	0.2%
	Total (calibration + output + daily)	**1.0%**

Impact of systematic shift in delivered dose:

Table 1 shows simulated change in clinical outcome caused by a systematic deviation in dose throughout the treatment for a variety of modelled cases for individuals and patient populations using commonly accepted parameter values fitted to clinical trial data.

Dose shift (%)	TCP						NTCP	
	Prostate				Head & Neck		Prostate	Head & Neck
	RT01 Trial		Fox Chase		PARSPORT		Rectum	Parotid
	Ind.	Pop.	Ind.	Pop.	Ind.	Pop.		
-3	-22.2	-10.8	-28.7	-17.3	-26.1	-10.2	-12.8	-4.2
-2	-14.1	-7.2	-18.6	-10.7	-16.7	-6.2	-8.5	-2.8
-1	-6.7	-2.7	-9.0	-5.1	-8.0	-3.8	-4.2	-1.4
0	0	0	0	0	0	0	0	0
1	6.1	2.3	8.2	4.7	7.1	3.1	4.1	1.4
2	11.4	6.1	15.6	8.6	13.5	7.0	8.1	2.8
3	16.2	9.0	22.1	12.1	19.0	9.2	12.0	4.1

Table 1: *Percentage change in outcome probability for different clinical cases. TCP was calculated for an individual patient with fixed alpha/beta ratio and a population included a variation in alpha/beta ratio across the patient cohort.*
'RT01' was a randomised controlled trial comparing 64Gy and 74Gy for prostate cancer [Dearnaley et al. 2014 The Lancet Oncology 15(4)_ 464-473].
'Fox chase' assessed a range of delivered doses to the prostate between 70-76Gy for medium risk prostate cancer [Hanks et el. 2002, Int. Jour. Of Radiat. Onc. Biol. Phys. 54(2) 427-435].
'PARSPORT' examined dose sparing of the parotid glands using conformal and IMRT. Here the doses from the IMRT plans are used as these are more comparable to modern treatment techniques [Nutting et al. 2011, The Lancet Oncology, 12(2) 127-136].

Impact of machine scheduling

The Fox Chase case, shows the greatest variation in TCP with 5th and 95th percentiles of 71.0% and 80.7% (range 9.7%). The RT01 prostate case and head and neck case had 5th and 95th percentiles of 52.5% and 58.9% (range 6.4%), and 60.1% and 66.8% (range 6.7%) respectively. See figure 1 for further details.

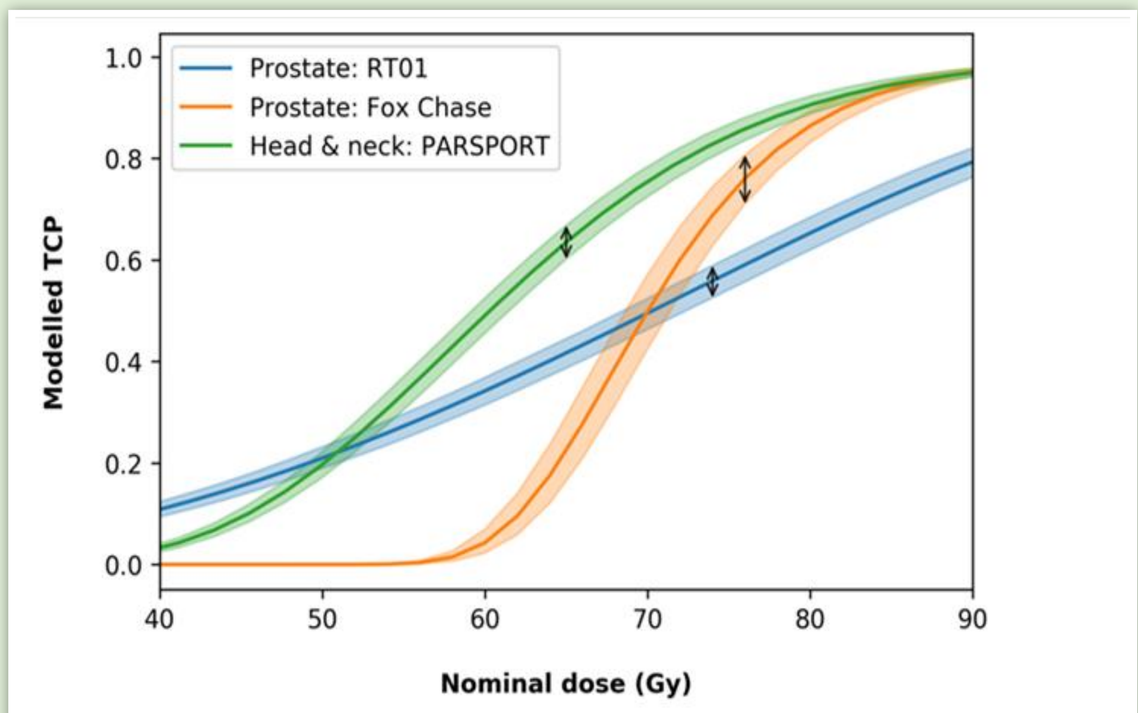

Figure 1: *The simulated variation in TCP for a cohort of patients with spreads in alpha/beta values for the clinical cases detailed in Table 1. The solid line indicates the mean values and shaded regions indicate 5th to 95th percentiles. Variation in this simulation arises solely due to the machine to which a patient is assigned.*

Comparison of conformal and IMRT dose variation: There is a greater variation in the planned dose to the target volume for a population of patients planned using conformal techniques than with IMRT. Values are compared in Figure 2.

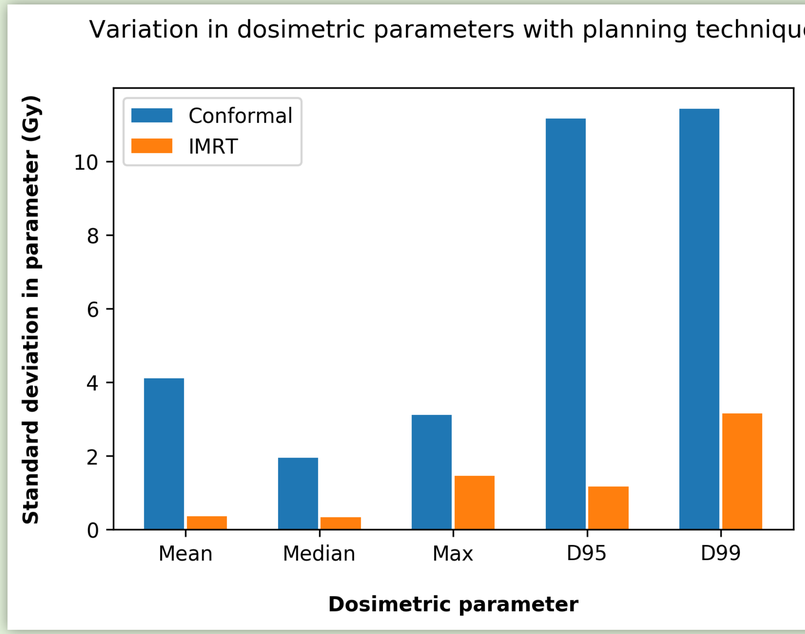

Figure 2: *Dosimetric parameter variation (SD) for a set of conformal and IMRT plans from the PARSPORT trial.*

The variation in planned target doses is significantly reduced when using IMRT techniques reducing variation (SD) in the mean dose from 4% to <0.5%.

Variation in planned target dose with conformal plans was greater than that arising from the dosimetry chain, with IMRT the variation in the dosimetry chain is now greater than that inherent in planning.

Conclusions

This analysis highlights the increased importance of accurate dosimetry particularly in the advent of greater treatment planning accuracy and consistency.

It may be desirable to review routine tolerances and reduce these below the common 2% used. Changes of this magnitude are readily detected; however this information is seldom used routinely even though easily available with data recorded electronically.

Clinical trials may benefit from reducing uncertainty in delivered dose to provide more robust assessments of response between trial arms

Key points:

- Variation in beam output due to drift is a large source of uncertainty in delivered dose.
- Consideration should be given to including this uncertainty within clinical trials.
- Tolerances for routine output checks should be reviewed in light of current QC recording and monitoring technologies available to ensure best use of the data.

References:
[1] Hanks et al. (2002) Radiat. Onc. Biol. Phys. 54(2) 427-435
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Full thesis available

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