

Tumour size measurements: impact of inter-operator variability on model-based drug effect evaluation

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Background and Aim

Tumour size (TS) measurements are commonly used to characterize disease progression in oncology clinical trials, evaluation of drug effects and for modelling.

However, TS measurements are subject to inter-operator variability which could lead to output misinterpretation [1] and therefore affect the future of patients in a trial, as well as the global drug-induced patient benefit determination.

Aim: to explore the inter-operator variability of tumour size measurements in a selected population of a phase III clinical trial and its impact on model-based drug effect evaluation at individual lesion level.

Data selection

Phase III clinical trial [2]

522 patients

Availability of two measurements of the same lesion on the same CT-scan at each time point

**Individual lesion longest diameter
M1 (Hospital) vs M2 (Centralised centre)**
122 lesions from 62 patients selected

Methods

A visual exploration was performed to identify trends within M1 and M2 profiles.

Linear regression and RERs (Equation 1) were used to explore the correlation between:

$$RER = \frac{M1 - M2}{M2} \times 100 \quad (\text{Equation 1})$$

$$TS(t) = TS(0) \times (e^{Kg \times t} + e^{-Kd \times t} - 1) \quad (\text{Equation 2})$$

RER, relative error ratio; TS(0), TS at baseline; Kg, growth rate; Kd, decay rate.

Results

3 different patterns (Figure 1) were present; M1 and M2 were either:

- Similar over time (23%) and so no impact will be observed on drug effect assessment.
- Different but follow the same trend (42%) and the difference would mostly affect estimated TS at baseline.
- Different and follow different trends (35%) and the difference would directly affect estimated drug effect.

M1 and M2 at each time point:

- Data were correlated with an $r^2=0.73$ (A), which is slightly low as M1 and M2 are based on the same “true value” and the only source of variability is the operator.
- The RERs were widely distributed from -91.7% and 1,200.0% with narrower 1st and 3rd quantiles (-13.4% to 28.5%) (B), close to the 15% variation observed by Hopper *et al.* [1].

M1 and M2 individual estimates:

- TS at baseline estimates were correlated ($r^2=0.71$) (C), which is similar to raw measurements.
- Drug effect estimates did not appear to be correlated ($r^2=0.27$) (D), surprisingly.
- However, population drug effect estimates were similar (RER < 15%), suggesting that interpretation of outcomes for a typical patient would be close.

Figure 1: Individual fits for TGI models classified by trend

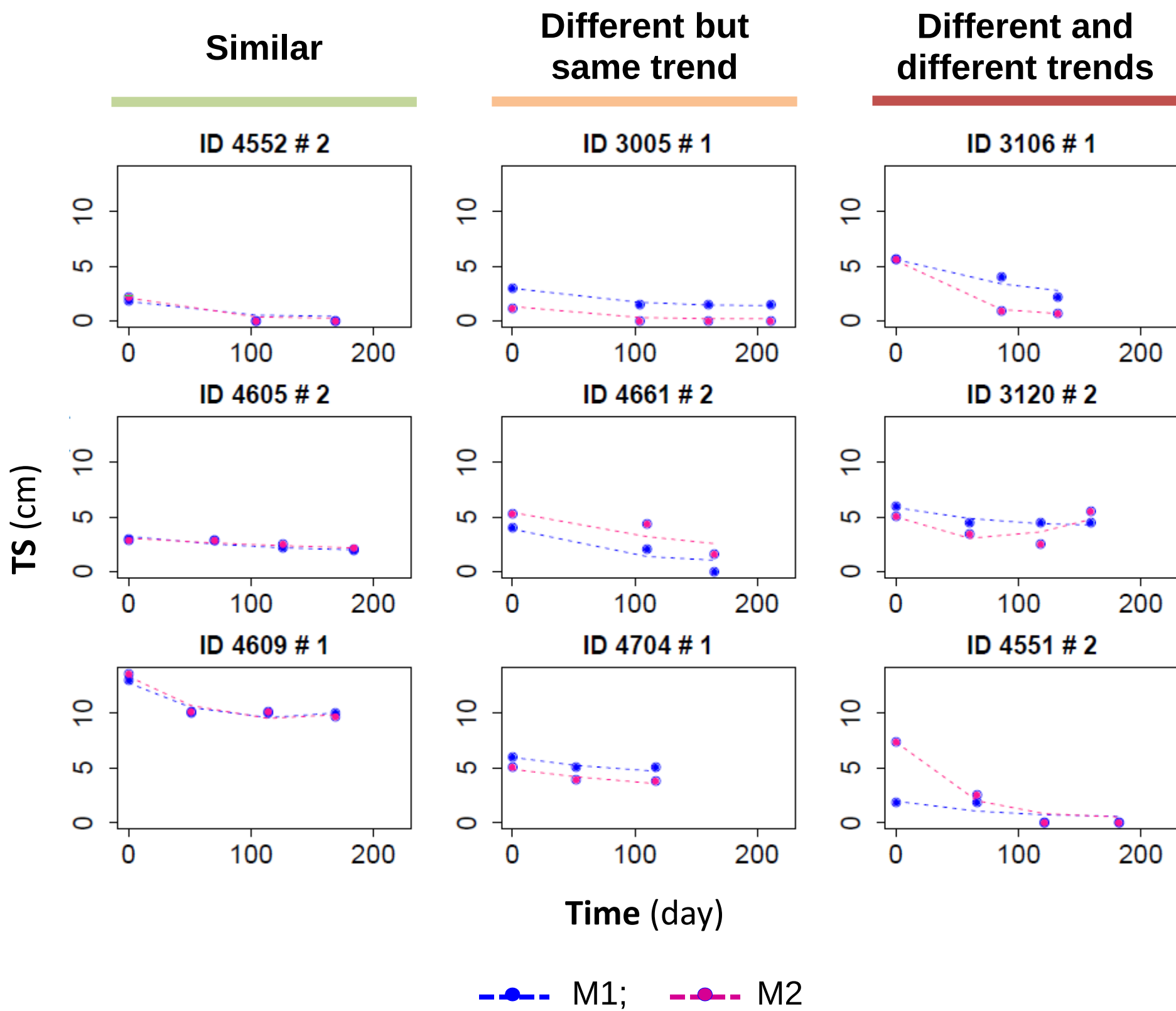
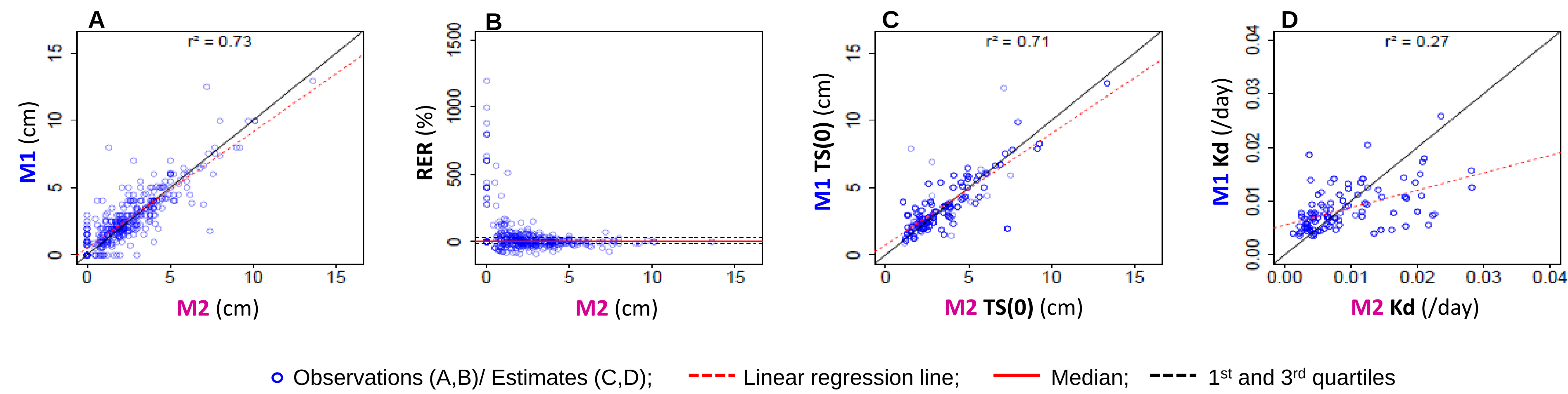


Figure 2: Correlation and RERs plots



Plots of correlation (A) and RERs (B) between M1 and M2 at each time point; plots of correlation between M1 and M2 model-based tumour size at baseline estimates (C) and drug effect (Kd) estimates (D).

Final parameters for TGI models

Parameters	Estimates (RSE%)		RERs
	M1	M2	
TS at baseline (cm)	3.1 (5)	2.9 (5)	6%
IIV	0.32 (14)	0.33 (12)	-
Growth rate (/day)	0.0011 (22)	0.00063 (45)	83%
IIV	0.27 (35)	0.64 (44)	-
Decay rate (/day)	0.0073 (11)	0.0064 (15)	14%
IIV	0.37 (38)	0.86 (33)	-
Additive residual error (cm)	0.48 (9)	0.43 (11)	11%

IIV: Interindividual variability; RSEs: relative standard errors.

Conclusions

This analysis revealed that **the operator can induce a wide variability** in TS measurements and this is therefore an important variable to consider.

The model-based interpretation of drug effect could be affected, especially at the **individual level**, as no correlation was observed between M1 and M2 individual drug effect estimates.

However, **drug-effect interpretation for a typical patient could be similar** as population parameters were comparable; suggesting that the global evaluation of drug efficacy by using modelling approaches might not be affected.

References

- [1] Hopper K, et al. Analysis of interobserver and intraobserver variability in CT tumor measurements. *AJR Am J Roentgenol.* 1996;167(4):851-4.
- [2] Sandler A, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* 2000;18(1):122-30.