

Background & Objectives

- The tyrosine kinase inhibitors erlotinib and gefitinib are among the treatments for non-small cell lung cancer (NSCLC). However their benefits are frequently limited by acquired resistance (e.g. secondary mutation in T790M). High-dose pulses with low-dose continuous therapy was proposed to address this^{1,2}.
- Our aim was to build a modeling and simulation framework for adverse events (AE) commonly encountered during erlotinib treatment, rash and diarrhea, to provide quantitative insights into erlotinib toxicity and the proposed dosing strategy.

Methods

Patients & Data

- AE data were available from 39 stage-IV NSCLC patients treated with erlotinib (150mg/day oral)³.
- Dates of AE incidence and resolution were recorded, and AEs were graded according to the National Cancer Institute-Common Toxicity Criteria (grade 1=mild, grade 2=moderate, grade 3=severe).

Rash	No. of patients suffering from at least one incident	23	Diarrhea	No. of patients suffering from at least one incident	18
	Total no. of incidents	76		Total no. of incidents	22
	Mild	33		Mild	19
	Moderate	34		Moderate	3
	Severe	9		Severe	0

Table 1. A summary of the rash and diarrhea incidents during and after erlotinib intake

Analysis, Model Development & Simulation Analysis

- A continuous-time Markov model with a compartmental structure (fig. 1) was developed. Probabilities of experiencing AE severities were modeled as compartment amounts. The likelihood was maximized to observe each set of states, and rate constants reflecting probability transitions between different states were estimated using NONMEM 7.3.
- Erlotinib exposure, mutational status of the cells, radiotherapy and co-medications histories, laboratory findings and demographics were investigated for their influence on AE.
- The AE models were coupled to a parametric time-to-death model accounting for the survival of patients.
- A simulation study (1000 virtual patients) using the models built was conducted to compare the toxicities of different dosing regimens (standard and pulsed regimens).

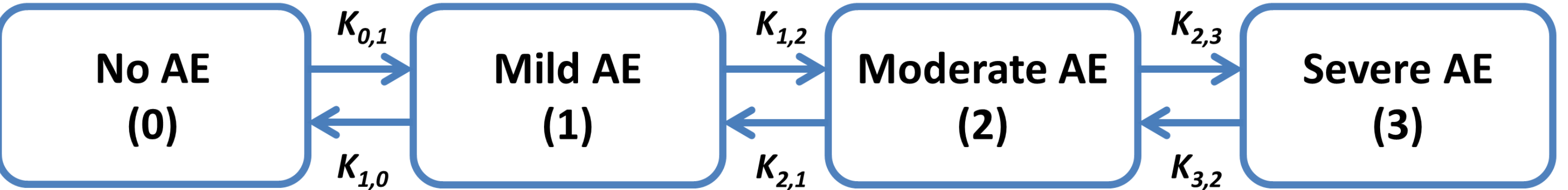


Fig.1. The compartmental model structure. Different compartments represent the different severities of adverse events (AE). Forward or worsening ($K_{0,1}$, $K_{1,2}$, $K_{2,3}$), backward or recovery ($K_{1,0}$, $K_{2,1}$, $K_{3,2}$) rate constants account for the transitioning of the patients between different AE states.

References

- Chmielecki J, et al. Sci Transl Med. 2011;3(90):90ra59.
- Foo J, et al. J Thorac Oncol. 2012;7(10):1583-93.
- Zander T et al. J Clin Oncol. 2011;29(13):1701-8.

Results

Rash

- Eq.1 described transitioning to higher rash grades. Radiotherapy decreased transition probability constants to higher rash grades by 81% (fig. 2). VPCs were adequate (fig. 3a)

$$K_{F,XY} = \text{BASE}_{XY} * e^{(-K_{TF} * \text{time})} * (1 - \text{RTX Effect} * \text{RTX}) + C_p * \text{SLOPE} \quad (1)$$

$K_{F,XY}$: Forward worsening transition probability constant, BASE_{XY} : baseline forward constant, K_{TF} governs the decrease of forward constants with time since starting erlotinib, RTX is 1 for radiotherapy, and zero for no radiotherapy, slope: parameter relating the transition constant to plasma concentration, CP.

- Recovery decreased exponentially with exposure [eq. 2].

$$K_{B,YX} = \text{BASE}_{YX} * e^{(-\text{BEXP} * C_p)} \quad (2)$$

$K_{B,YX}$: Backward recovery transition probability constant, BASE_{YX} : baseline backward constant, BEXP: parameter relating the transition constant to CP.

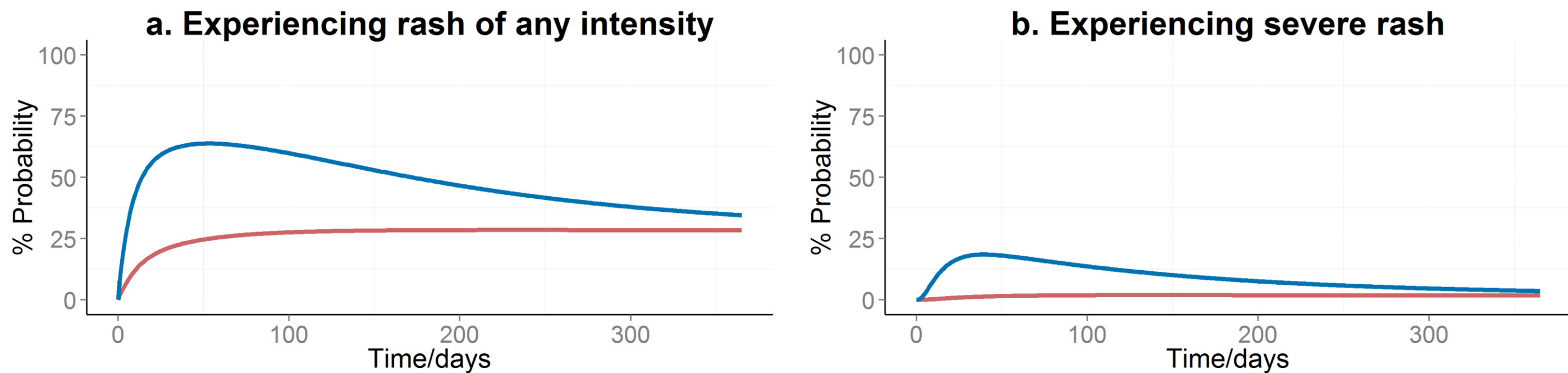


Fig. 2. Temporal courses of the probabilities of experiencing a) any rash intensity, b) severe rash. The figures show the attenuating effect of radiotherapy prior or during erlotinib treatment (red) in comparison to other patients (blue).

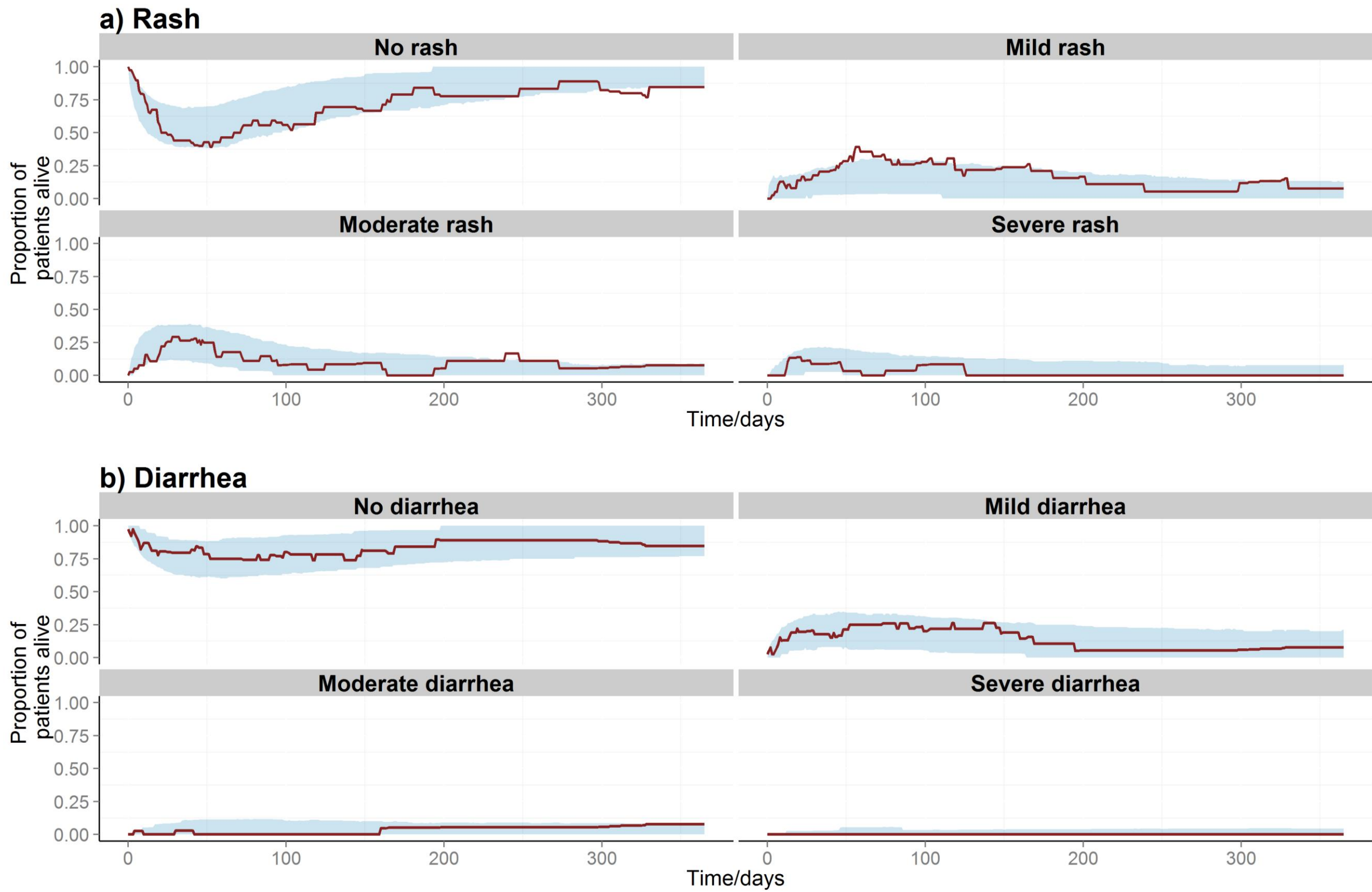


Fig.3. VPCs (1000 datasets) showing the proportions of alive patients experiencing each grade of a) rash or b) diarrhea. Solid red lines represent observed data, and the corresponding 95% prediction intervals based on the simulations are shown as shaded blue regions.

Diarrhea

- Erlotinib exposure was not found to significantly increase the risk of having diarrhea. The intrinsic risk was found to decrease exponentially with time. VPCs are shown in fig. 3b.

Simulation

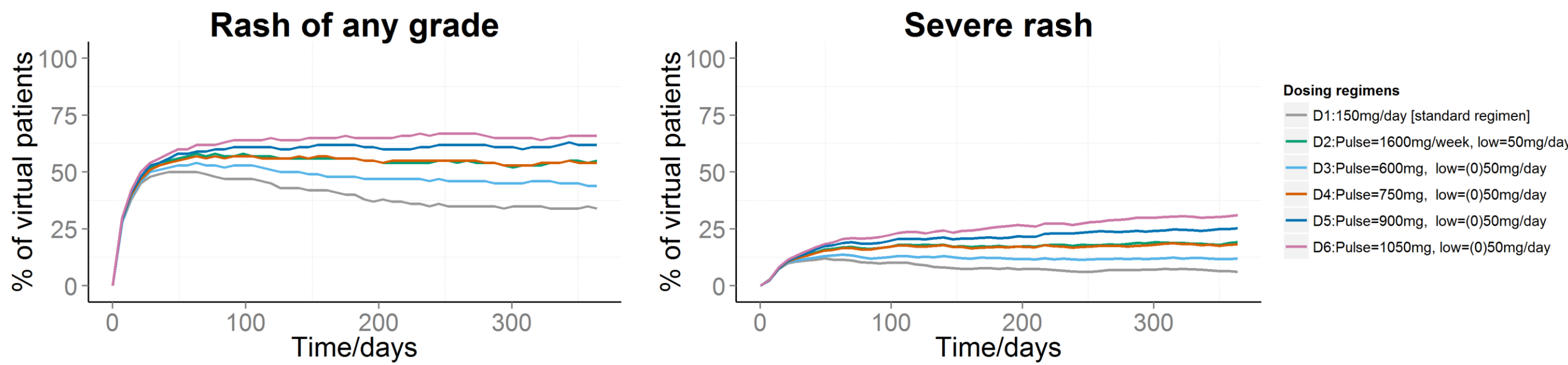


Fig. 4. Simulated profiles of the patients' proportions suffering from any rash grade (left) or severe rash (right) for different regimens. "Pulse" is the weekly dose, and "low" is the dose administered the rest of the week. D3-D6 have the pulses administered the first 2 days of the week.

Conclusions

- The framework predicted the tolerability of pulsed erlotinib dosing regimens.
- Radiotherapy mitigates erlotinib-induced rash, and might potentially be used with erlotinib simultaneously for treating NSCLC.