

Building of virtual geriatric cancer populations for physiologically-based modelling and simulation in cancer patients greater than 70 years of age



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Introduction

Physiologically-based pharmacokinetic (PBPK) models of anticancer drug disposition allow for simulation of the effects of changes in dose and dosing interval in various age groups and therefore may assist in dose and dosing regimen selection.

Although the elderly comprise the majority of cancer patients¹, they are under-represented in clinical trials of anticancer agents^{2,3}, particularly in Phase I trials in which doses are determined. This lack of inclusion may be one of the reasons they have a higher incidence of side effects and toxicity from chemotherapy.

PBPK modelling and simulation in the elderly requires a virtual geriatric population containing information on parameters that may affect PK that are known to change with advancing age, such as gastric emptying, liver volume, liver blood flow, and renal function.

In addition, physiological changes affecting PK may occur in cancer as a result of disease and/or drug treatments. Parameter differences seen in cancer include elevations in alpha-1 acid glycoprotein (AAG), an acute phase reactant that binds neutral and weakly basic drugs, including docetaxel, paclitaxel, imatinib, and erlotinib, and decreases in albumin and haematocrit⁴. In addition, different height and weight distributions may be present in relation to age as compared with healthy elderly patients.

Whether physiological changes that potentially affect PK will change by cancer type as well as with age is not known. Here we report the results of our initial analysis of basic physiological and laboratory parameters that are likely to impact on PBPK modelling in non-small cell lung and gynaecological cancer patients ages 70 and over as compared with healthy simulated geriatric individuals in the same age range.

Methods

- Anonymised patient data/plasma samples were obtained from 163 non-small cell lung cancer (NSCLC) patients aged 33-81 years
- Anonymised patient data was obtained from 333 gynaecological cancer patients (over 99% of whom were ovarian cancer patients) aged 24-89 years
- 300 simulated healthy geriatric individuals (145 female, 155 male, ages 70-89) were generated using the Sim-Geriatric NEC population in Simcyp version 15.1 (Simcyp Limited, Sheffield, UK)
- AAG concentrations were measured in NSCLC patient plasma samples by ELISA (Abcam, Cambridge, UK)
- Relationship between glomerular filtration rate (GFR) and age was assessed by nonlinear regression using GraphPad Prism version 6.05 for Windows, GraphPad Software, La Jolla, California, USA, www.graphpad.com
- Comparison of patient data by population was performed either by ANOVA with Tukey's multiple comparison's test (when parameters in all groups were normally distributed) or by the Kruskal-Wallis test with Dunn's multiple comparison's test (when any parameters were not normally distributed), also using GraphPad Prism version 6.05. Two-sided p-values are given.
- Using data from the analyses, a virtual ovarian cancer population was created within Simcyp version 15.1 and simulations were performed and compared with those using the Sim-Geriatric NEC population.

Results

- ❖ Patient subsets aged 70 years and over were extracted from the data sets and are described in Table 1, along with mean parameter values:

Parameter (mean ±SD)	NSCLC n=47 (26M, 21F)	Gynaecological n=113	Healthy Geriatric n=300 (145M,155F)
Age range (years)	70-81	70-89	70-89
GFR (mL/min)	Males: 79.4 ±27.3 Females: 60.3 ±16.8	57.4 ±20	Males: 82.6 ±22.6 Females: 65.8 ±23.9
Albumin (g/L)	38.9 ±4.71	37.3 ±6.54	43.3 ±4.31
AAG (g/L)	3.29 ±1.3	-----	0.795 ±0.143
Haematocrit	Males: 0.362 ± 0.054 Females: 0.364 ± 0.037	0.355 ±0.040	Males: 0.429 ±0.029 Females: 0.377 ±0.027
Weight (kg)	Males: 80 ±7.96 Females: 69.1 ±13.7	67.8 ±13.2	Males: 80.2 ±12.5 Females: 67.3 ±12.4

Table 1. Ages 70+ subsets of population data

Results – cont'd

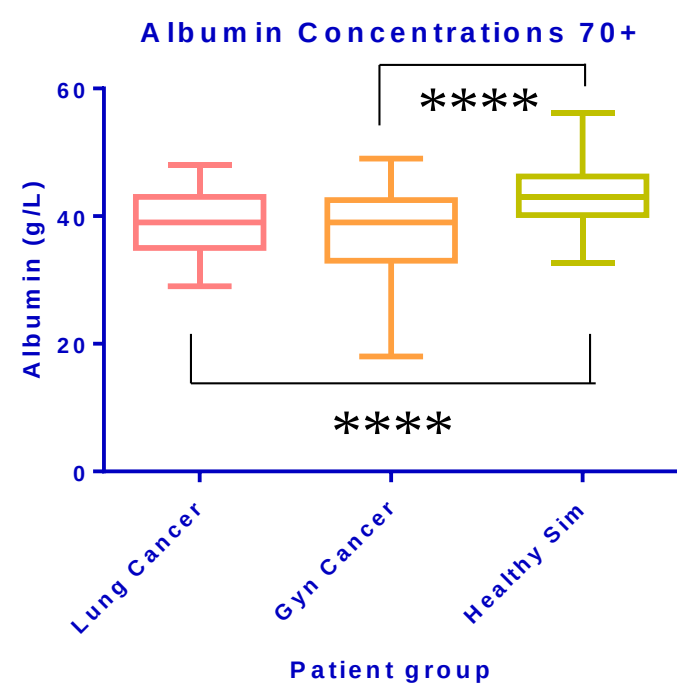


Figure 1. Albumin concentrations between groups

Plasma albumin concentrations in lung and ovarian cancer patients aged 70+ were lower than those of simulated healthy geriatric patients in the same age range

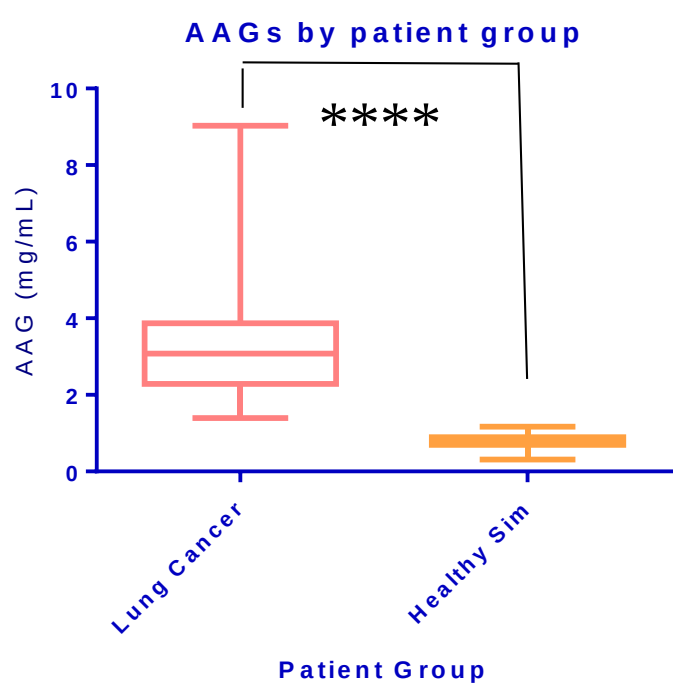


Figure 2. AAG concentrations between groups

Plasma AAG concentrations in lung cancer patients aged 70+ were higher than the normal range and higher than those of simulated healthy geriatric patients in the same age range

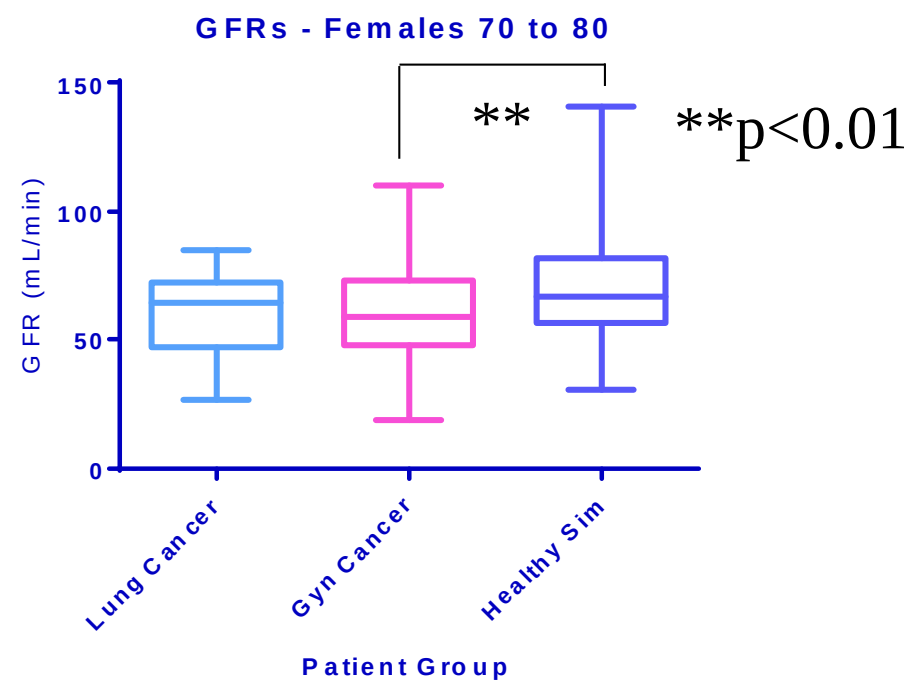


Figure 5. GFRs between groups--females

GFRs were lower in female gynaecological cancer patients aged 70-80 than in healthy simulated patients of the same sex and age range

Haematocrits were lower in female ovarian cancer patients aged 70+ and in male lung cancer patients than in healthy simulated patients of the same sex and age range (data not shown)

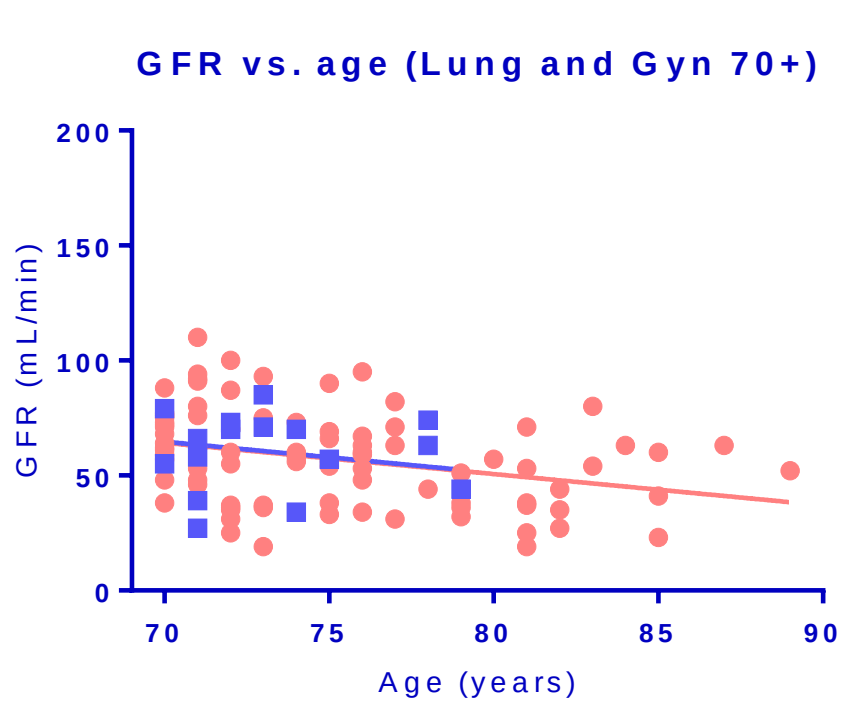
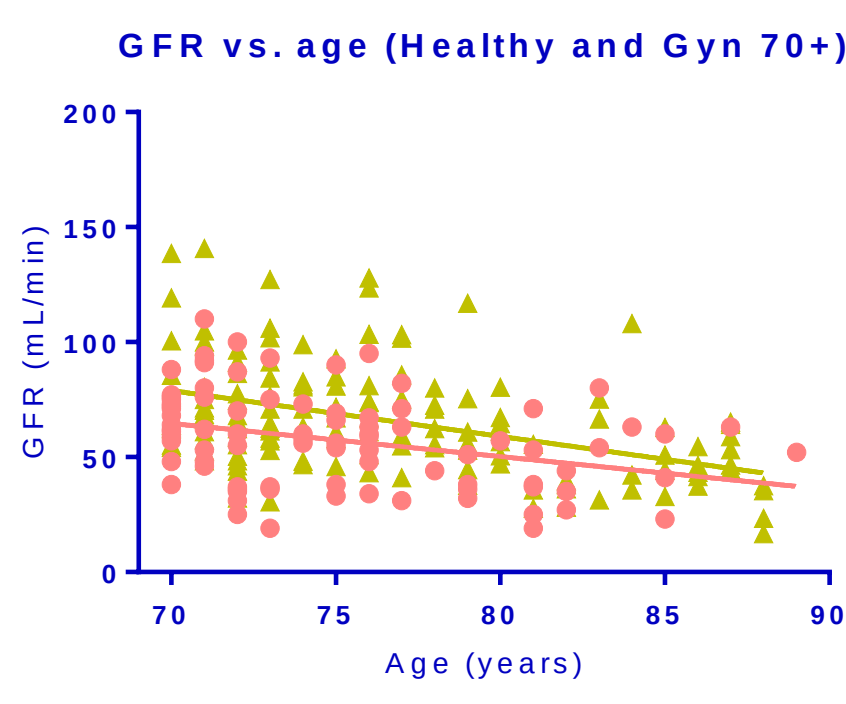
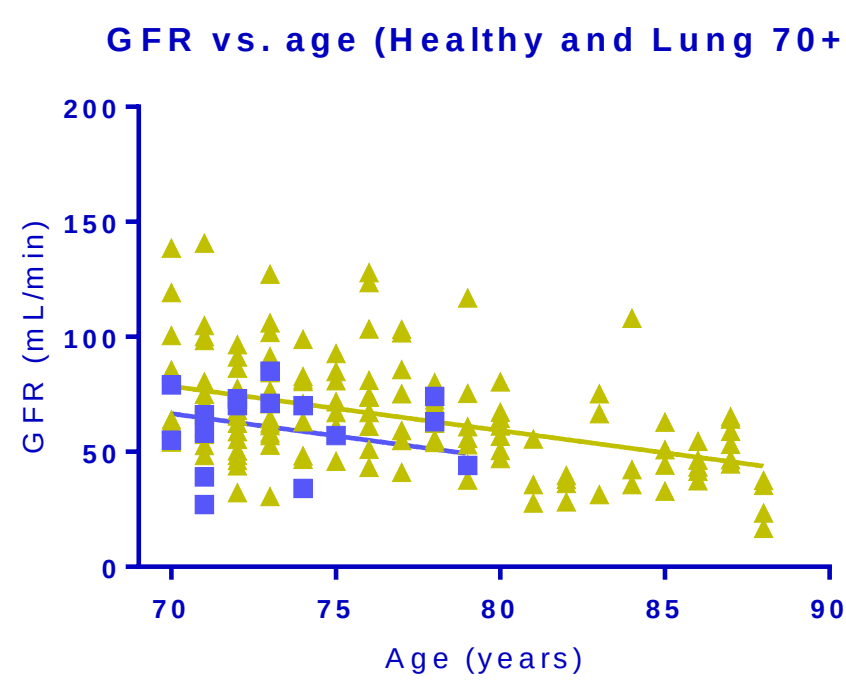


Figure 7. GFR vs. age comparisons between female groups



Lung cancer $r^2=0$ Gyn cancer $r^2=0.120$ Healthy $r^2=0.196$

GFR (as measured directly by radioisotope) showed an age-related decline but no significant difference in slopes of regression lines was observed between groups

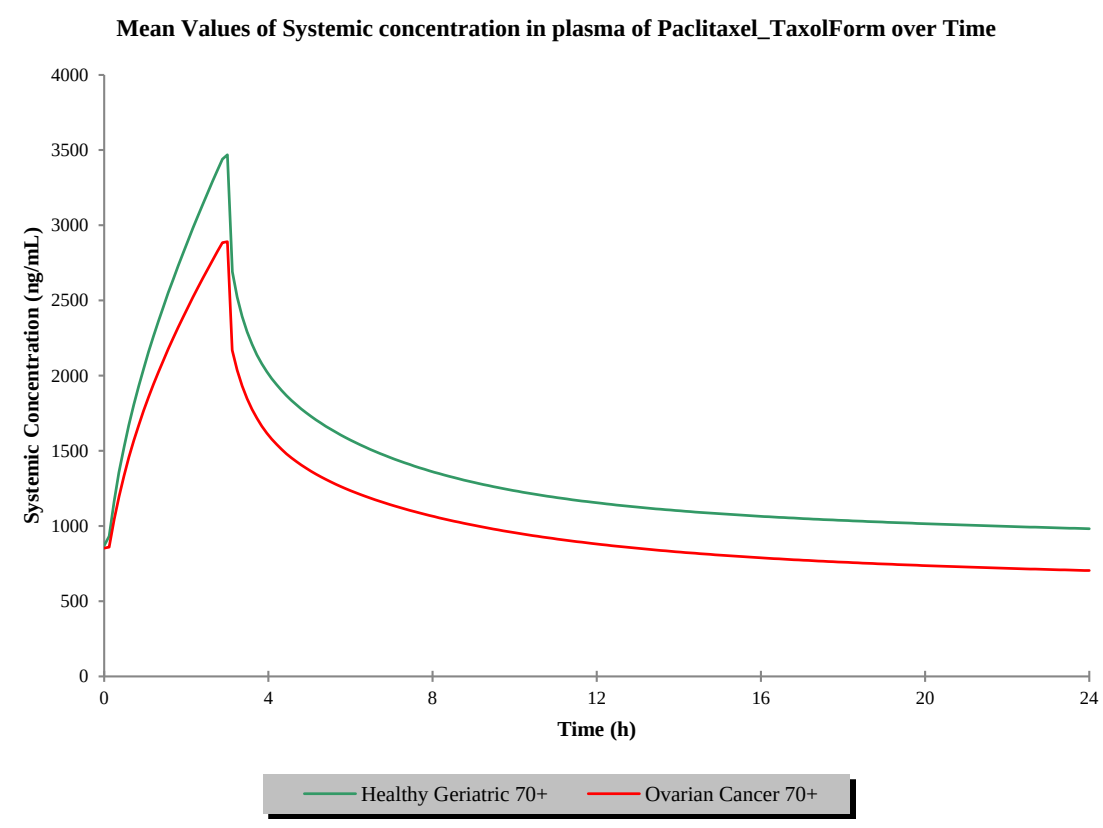


Figure 8. Simulated paclitaxel infusion concentration-time profiles in healthy females and virtual ovarian cancer patients

Healthy		Ovarian	
PKPD Parameters	Mean	PKPD Parameters	Mean
CL (L/h)	1.76	CL (L/h)	2.43
V _{ss} (dL/kg)	3.67	V _{ss} (dL/kg)	5.15
PKPD Profiles	Mean	PKPD Profiles	Mean
C _{Max} (ng/mL)	3486.69	C _{Max} (ng/mL)	2920.37
T _{Max} (h)	2.97	T _{Max} (h)	2.96
AUC ₀₋₂₄ (ng/mL·h)	33499.98	AUC ₀₋₂₄ (ng/mL·h)	20754.44
CL _{ss} (Dose/AUC) _{ss} (L/h)	9.18	CL _{ss} (Dose/AUC) _{ss} (L/h)	11.80

A preliminary simulation of a 3-hour infusion of paclitaxel at a dose of 175 mg/m² showed difference in PK profiles

Conclusions/Future directions

- Incorporation of parameter differences such as GFR, AAG, albumin, and haematocrit into virtual cancer populations is likely to have a significant effect on PBPK simulations of some anticancer agents
- Future directions
 - Continued analysis of the effect of cancer type/drug treatment/stage of treatment/disease stage on patient covariates is needed
 - Creation of a lung cancer population file within Simcyp and continued validation of PBPK models of paclitaxel and carboplatin in this population will be done
 - Further analysis will determine the necessity of building cancer type-specific virtual cancer populations

References

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