The Utility of Pharmacokinetic Parameters in Predicting Disease Free Survival

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Introduction Pharmacokinetic modelled parameters have been used by a number of authors to attempt to predict an individuals response to radiotherapy and chemotherapy. In a number of cases pharmacokinetic parameters have demonstrated differences between eventual responders and non-responders prior to[(1-3)] and early[(4-8)] during treatment. However all of these results are concerned with short-term treatment response and not longer term survival. The aim of this paper is to determine the utility of pharmacokinetic parameters in predicting longer term disease free survival in breast cancer patients compared to traditional survival indicators.

Methods In sixty-eight breast cancer patients pharmacokinetic parameters transfer constant (K^{trans}), rate constant (K_{ep}), and the extracellular extravascular space (V_e) were calculated prior to treatment using a two compartment pharmacokinetic model based on the Brix model[(9)]. Pharmacokinetic parameters were calculated for a 3x3 pixel 'hot-spot' from within a lesion encompassing ROI. For all pharmacokinetic parameters <median values were compared to ≥median for statistical analysis of survival.

Pre-treatment biopsy tissue was used to provide oestrogen receptor (ER) status (negative or positive), progesterone (PR) status (negative or positive), nodal status (negative or positive), tumour type (special type or no special type) and grade (I and II or III), while MRI data provided tumour size (<median vs. ≥median). These parameters acted as traditional survival indicators.

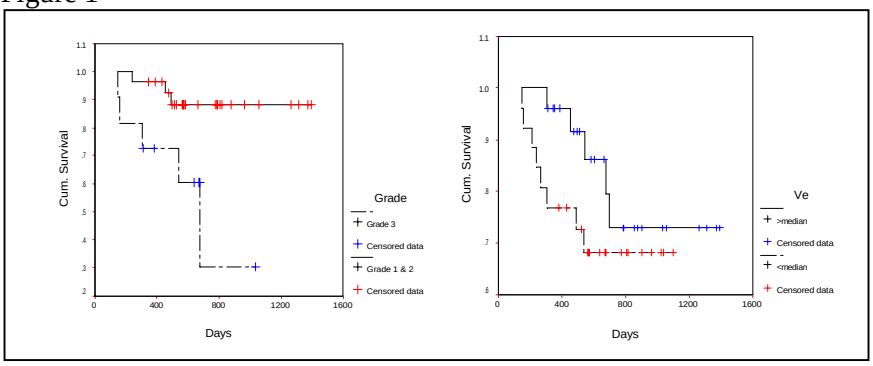
Treatment failure (critical event) was defined as tumour remission and/or metastasis, whilst data from patients without treatment failure was treated as censored. Kaplan-Meier survival plots were generated for each parameter, while group comparisons were made utilising logrank tests.

Results Sixteen patients were lost to follow-up. 14 patients suffered a treatment failure and 38 patients were censored. The median follow-up time was 594 days, range 147 to 1391 days. The results of logrank tests for ER, PR, tumour grade, tumour type, tumour size, K^{trans}, K_{ep} and V_e are presented in table 1. Kaplan-Meier survival plots are presented in figure 1 for the best performing traditional survival indicator and the best performing pharmacokinetic parameter.

Table 1

Parameter	N	P value
ER	42	0.0166
PR	41	0.0251
Nodes	52	0.0589
Tumour Type	45	0.7165
Tumour Grade	39	0.0078
Tumour Size	52	0.0364
K^{trans}	52	0.8194
K_{ep}	52	0.3430
V_e	52	0.2608

Figure 1



Conclusion These results indicate that for this cohort of patients for this follow-up interval that pharmacokinetic modelled parameter do not perform as well as traditional survival indictors. However the follow-up time was relatively short (median 594 days; range 147 to 1391 days) for survival studies. Likewise there were a large number of censored cases. Therefore this cohort of patients will be followed for a longer time period to ensure the validity of these results.

References [1]Hayes C et al NMR In Biomedicine 15(2):154-163, 2002. [2]George ML et al B J Surgery 88(12):1628-1636, 2001. [3]Yamashita Y et al Radiology 216(3):803-809, 2000 [4]Wasser K et al Euro Radiology 13(1):80-87, 2003 [5]Delille JP et al Radiology 228(1):63-69 2003, [6]Hawighorst H et al JMRI 8(4):783-788, 1998 [7]Galbraith SM et al Journal of Clinical Oncology 21(15):2831-2842, 2003 [8]Wasser K et al Euro Radiology 13(6):1213-1223, 2003 [9]Brix et al Journal of Computed Assisted Tomography 15(4):621-628, 1991

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