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Individualized predictions of disease progression following radiation therapy for prostate cancer.

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Background: Following treatment for localized prostate cancer, men are monitored with serial PSA measurements. Refining the predictive value of post-treatment PSA determinations may add to clinical management and we have developed a model that predicts for an individual patient future PSA values and estimates the time to future clinical recurrence.

Methods: Data from 934 patients treated for prostate cancer between 1987 and 2000 were used to develop a comprehensive statistical model to fit the clinical recurrence events and pattern of PSA data. A logistic regression model was used for the probability of cure, non-linear hierarchical mixed models were used for serial PSA measurements and a time-dependent proportional hazards model was used for recurrences. Data available up to February 2001 and September 2003 was used to assess the performance of the model.

Results: The model suggests that T-stage, baseline PSA, and radiotherapy dosage are all associated with probability of cure. The risk of clinical recurrence in those not cured by radiotherapy is most strongly affected by the slope of the long-transformed PSA values. We show how the model can be used for individual monitoring of a patient's disease progression. For each patient the model predicts, based upon his baseline and all post-treatment PSA values, the probability of future clinical recurrence in the validation dataset and of 406 PSA measurements obtained 1-2 years after February 2001, 92.8% were within 95% prediction limits from the model.

Conclusions: This statistical model presented accurately predicts future PSA values and risk of clinical relapse. This predictive information for each individual patient, which can be updated with each additional PSA value, may prove useful to patents and physicians in determining what post-treatment salvage should be employed.

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Keywords: Prostate cancer, PSA slope, Biochemical recurrence, Clinical recurrence, Joint longitudinal-survival models.

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1 Introduction

Widespread use of early detection programs for prostate cancer has led to earlier diagnosis followed by definitive local therapy as a means for treatment for many men. The hope with such early diagnosis and treatment is that it will increase cure rates and improve survival. Despite the shift to earlier treatment, a substantial percentage of patients treated with definitive local therapy show evidence of biochemical (PSA) recurrence within ten years following treatment. Analysis of the natural history of progression following local therapy and biochemical recurrence has shown that there is marked variation in the interval between PSA recurrence and evidence of clinical disease progression (e.g. distant metastases or local recurrence). It is clear that PSA monitoring following local treatment has created a large cohort of patients with a rising PSA as their only manifestation of disease. It is presently unclear whether or not an isolated elevation or modest rise in PSA following definitive therapy represents an indication or justification for treating patients with additional forms of therapy, commonly androgen ablation. Simply treating all patients with biochemical recurrence could lead to costly time-intensive and presumably unnecessary treatment of many patients. Thus there is a great need for a better understanding of the implications of a pattern of rising PSA.

In an effort to provide more rational selection of patients who are at high-risk for early disease recurrence following local therapy clinical models designed to predict or stratify patients based upon clinical, pathological and biochemical criteria have been developed (Kattan et al, 1999; Kattan et al, 2000; Kattan et al, 2000; D'Amico et al, 1999). These models have primarily focused upon prediction of biochemical recurrence following therapy, based on information available at the time of initial therapy, and have not entertained the possibility of prediction for patients at high risk for disease recurrence based on post-treatment PSA values. Models are greatly needed which can best predict those patients at high risk of early development of clinical recurrence following a pattern of rising PSA for initiation of salvage therapy and rational enrollment into clinical trials. Such models would be useful to accurately identify at an early time those men who are at high-risk

of early recurrence and who may benefit from salvage treatment (Kuban et al 1998, D'Amico et al 2003). Such models would also be useful to identify those unlikely to need therapy in the near future.

An important question in the treatment of prostate cancer is determining recurrence after radiation therapy for local disease. The correlation between changes in PSA and prostate cancer clinical recurrence (local recurrence or distant metastases) has been long recognized. Clinical recurrence is distinct from biochemical recurrence and elevations of PSA levels can precede clinically detectable prostate cancer recurrence by several years. A consensus on what constitutes a dangerous rise in PSA and how to translate it into guidelines for clinical monitoring has not been fully reached. Defining biochemical recurrence based on a series of PSA measurements has been a problematic and controversial topic. Radiation reduces PSA, but not to an undetectable level, then at a later time it may start to increase before any clinical evidence of disease is detectable. In contrast to the undetectable levels of PSA after successful radical prostatectomy, there is considerable variability in the amount by which PSA is reduced by radiation therapy, and the time interval before it starts to rise, if it does rise, and the rate at which it rises (Zagars and Pollack 1993).

To provide some uniformity to the way that rises in PSA following irradiation had been utilized, the American Society for Therapeutic Radiation Oncology developed a consensus definition of biochemical recurrence (ASTRO 1997). The definition was based on three consecutive rises in PSA. Although this definition is known to have a number of problems, (Horwitz et al 1996, Vicini et al 1999, Hanlon et al 2000, Taylor et al 2001, Horowitz et al 2003, Thames et al 2003) it did provide a benchmark against which alternatives could be compared. The primary use of the ASTRO definition is for consistency in comparing the results between different studies. It is less useful for monitoring an individual patient and for deciding on the initiation of hormonal therapy or other salvage therapy. Such decisions will usually be based, in the absence of clinical symptoms, on the value and the rate of rise of PSA, together with other factors such as the patient's age and stage and Gleason score of the tumor.

The purpose of this paper is to demonstrate a means to provide quantitative information, by way of a statistical model, about the likely future course of disease for a patient. This information can be used to enhance the medical decision making process. The quantitative information we provide will be derived from a large series of patients treated at the University of Michigan. We consider two aspects to the future progression of the disease, one is the predicted PSA pattern and the other is the occurrence of clinical events, such as local recurrence or distant metastases, indicating definitive disease, typically requiring additional therapy.

Any statistical model that is to be used for prediction must adequately capture the variation which is observed in PSA data and in the timing of clinical recurrences. This variation means that there will be uncertainty in any prediction, the model will also provide uncertainty ranges associated with those predictions. Thus, even though two patients could have the same prediction, the uncertainty associated with the prediction could differ and consequently the clinical decision about initiating further therapy could also differ.

Many previous papers on PSA profiles after radiation therapy have focussed on identifying features of the pattern which are important or prognostic. Examples of this are rise above nadir, doubling time or the ASTRO definition of recurrence. This can be regarded as leading to a two-stage approach, in which one first decides whether the data for a patient exhibits this summary feature, then one makes explicit or implicit predictions about the likely future course of disease. In this paper we bypass the intermediate step of consideration of specific features, instead we directly make predictions about the likely future course of disease based on all the available data, including all post treatment PSA values. Thus we demonstrate that, although consideration of summary intermediate features is convenient, it is not necessary to make predictions.

2 Material and Methods.

2.1 Patients.

2.1.1 Analysis dataset.

The data consist of 934 patients with localized prostate cancer, who were treated with external beam radiation therapy at the University of Michigan and affiliated institutions between July 1987 and February 2000. This patient series has been previously described (Sandler et al 2000, Symon et al 2003). The collection of these data were approved by the University of Michigan Institutional Review Board. Patients were excluded from this analysis if they received planned hormonal therapy before the end of the radiation therapy regimen, or if they had missing information on T-stage, pretreatment PSA or Gleason grade. No patient had a prostatectomy. The percentage of tumor stages 1, 2 and 3-4 were 29%, 62% and 9% respectively. The percentage in Gleason score 5 or less, 6, 7 and 8 or more were 27%, 32%, 32% and 9% respectively. Pretreatment PSA ranged from 0.3 to 229 with a median of 8.2. The patients ages at time of radiation ranged from 41 to 90 with a median of 71, the total dose ranged from 61Gy to 80Gy with a median of 69Gy and the overall treatment time ranged from 43 days to 94 days with a median of 54 days. The radiation was delivered using 3D conformal techniques as described elsewhere (Sandler et al 2000). Post treatment PSA was measured at approximately 6 month intervals. The median number of PSA values per patient was 6 (range 1-29). The total number of PSA measures is 6150. The maximum time between treatment and a PSA measurement is 145 months. During the follow-up period, up to February 2001, 140 patients experienced clinical recurrences, 65 had local recurrence, 70 had distant metastases and 5 had regional failure as their first clinical recurrence. Of the 794 censored patients, 144 died of other causes before any clinical recurrence and 650 were censored at February 2001 or were lost to follow-up prior to that date. The median follow-up time was 44 months. Fifty nine patients received hormonal therapy prior to any clinical recurrence, of these 15 had a later clinical recurrence.

2.1.2 Validation dataset.

The validation dataset consists of all data collected on these 934 patients after February 2001 and available in September 2003. We focus on the 612 patients who were alive at the last contact time in the analysis dataset, and were not known to have experienced a clinical recurrence or received hormonal therapy prior to February 2001. There were 541 patients where new follow-up information was available. Amongst these 541 patients, 472 were alive at the end of the this new follow-up, 63 died from other causes not related to prostate cancer and 6 died from prostate cancer. The median additional follow-up time is 30 months. There were 329 patients with additional PSA values, these patients provided 999 PSA measurements within three years of the previous last follow-up date. Fifteen of the patients developed clinical recurrence in the new follow-up period, 6 of these 15 had HT before the recurrence, an additional 14 have received HT without any clinical recurrence.

2.2 Statistical Methods.

We use a comprehensive statistical model to fit the clinical recurrence events and pattern of PSA data. The model used in this paper is an adaptation and enhancement of the model previously described in Law et al (2001), and Yu et al (2003). In this paper the model is used to fit the data in the analysis dataset and to make predictions of future clinical events and future PSA values for individual patients. These predictions are then compared with the real data from the validation dataset.

The statistical model requires three components, one to model the possibility of cure, one to model the serial PSA measurements and one to model the hazard of a clinical event. A brief description is given below, with a fuller description in the Appendix. A logistic regression model was used for the probability of cure. We assume that the log-odds of the probability of cure is a linear combination of the baseline covariates, T-stage, Gleason, PSA, total dose, treatment duration and Age. Non-linear hierarchical mixed models were used for serial PSA measurements. The longitudinal model for PSA for person i at time t is based on $PSA_i(t) =$

$a_i exp(-b_i t) + c_i exp(d_i t)$, (Kaplan et al 1991, Cox et al 1993). The first term represents the slow decrease in PSA after radiation, the second term represents the increase in PSA due to tumor regrowth. For cured patients we assume d_i is close to zero. The coefficients (a_i, b_i, c_i, d_i) can differ from one person to the next and they are also allowed to depend on baseline covariates. A time-dependent Cox proportional hazards model was used for the clinical recurrence events. During the follow-up period the hazard of recurrence for non-cured patients was assumed to depend on the current PSA, current slope of PSA, an indicator of whether salvage hormonal therapy was given and baseline covariates. The model described above is designed to include population average trends, to allow for between-patient heterogeneity in response which can be explained by baseline patient and treatment variables, and to allow for extra unexplained heterogeneity in PSA and clinical response.

PSA data after hormonal therapy is not used in fitting the model, but clinical recurrences after hormonal therapy are used. The model is fit using Markov Chain Monte Carlo (MCMC) methods, as described in Yu et al (2003). We present results of odds-ratios from the cure model and relative hazards from the Cox model.

The model is used for the prediction of a future PSA value for patient i at any future time T. In addition we give the 2.5th to 97.5th percentile range of predicted values. For the prediction of future clinical events the probability that patient i is event-free T months into the future can be calculated from the equations describing the model. Both the average probability and the range of probabilities are presented graphically. We only predict future PSA values and clinical events for patients who are alive at last follow-up, have not had a clinical recurrence or received hormonal therapy. These predictions are compared with the data in the validation dataset. We also present graphically the estimated possible impact of hormonal therapy on each patient's time to clinical recurrence. This is calculated using the model under the assumption that the patient starts hormonal therapy at the time of last contact.

3 Results.

The parameter estimates for the cure part and the hazard part of the model are presented in Tables 1 and 2. The results for the cure model part suggest that T-stage, baseline PSA and Total Dose are all associated with the probability of cure in the expected direction. Treatment duration and Gleason score are at most weakly associated with the probability of cure. For the hazard of clinical recurrence model for the non-cured group, by far the most important variable is the slope of PSA, other important variables are hormonal therapy, baseline PSA and Gleason score. Interestingly the current value of PSA is not associated with the hazard of clinical event when the other variables are included in the model. The specific results regarding the association between the covariates and the pattern of PSA are not presented, the most interesting are that higher T-stage, baseline PSA and Gleason are all associated with a faster rate of increase of PSA in the non-cured group.

Figure 1 shows the pattern of PSA and the predicted probability of future clinical recurrence from the date of last contact, with and without the addition of hormonal therapy at the last contact time, for three selected patients with long follow up times. The patients were selected to illustrate a range of PSA patterns and predictions. The magnitude of the potential impact of hormonal therapy (HT) can be seen. The right hand half of the figure shows the uncertainty of the prediction of clinical recurrence, without HT. For patients (a) and (b) there is a clear pattern of increasing PSA, suggesting eventual clinical recurrence. Patient (a) has a steeper rise than patient (b) which leads to a higher probability of recurrence within 4 years. For patient (c) the favorable pattern of PSA post-treatment suggests cure, which corresponds to the almost horizontal predicted clinical recurrence curve, however there is a small probability of eventual recurrence (0.05) as seen in the uncertainty curves. Figure 2 shows the pattern of PSA and predicted probabilities of clinical recurrence for 3 patients with short or medium follow-up times. Patient (d) has an almost level pattern of PSA but with a suggestion of an increase at the end of his follow-up. Thus there is considerable uncertainty about the future for this patient, this

is reflected in the right hand half of the figure. It shows horizontal curves reflecting cure (with probability 0.63) and decreasing curves reflecting eventual recurrence (with probability 0.37). Patient (e) has a clearly rising pattern of PSA, even though the values are low, this leads to significant probability of recurrence within 4 years. Patient (f) has very short follow-up leading to considerable range of predicted probabilities of recurrence within 4 years. It is also worth noting that despite a clearly increasing pattern of PSA for some of the patients in Figures 1 and 2, for none is the predicted probability of recurrence within 4 years greater than 50%. We envision that graphs such as these could be useful to the clinician and the patient is deciding whether to initiate HT, or when PSA should next be measured.

Figure 3 shows predicted and observed future values of PSA for the six selected patients. The shaded areas represent 95% prediction intervals for each patient, these are derived from the model fit to the PSA data (as shown by the dots). We note that patients (a), (b) and (c) who have lots of data have fairly narrow prediction intervals, whereas patient (f) has less follow-up and thus a wider prediction interval. We envision a graph like this would also be useful in monitoring the progression of the patient, for example if a new PSA value is measured and it falls outside the shaded region then this is indicative of the patient doing either worse than or better than expected. After a new measurement is obtained a new graph could be produced, thus giving real-time monitoring of a patient's progression.

The + symbols in the graphs are PSA measurements obtained from the validation dataset for these 6 patients, all the values fall within the 95% prediction intervals. We note that none of these 6 patients has had a clinical recurrence in the validation dataset follow-up period. Table 3 shows the proportion of future PSA values amongst all available future data which were within the 95% prediction intervals, we see very good correspondence with the expected 95% level for all years.

Table 4 compares the predicted clinical recurrence with the observed data on clinical recurrences and salvage hormonal therapy. For each of the 541 validation patients, the probability of clinical recurrence within three years after the last contact date is calculated, and divided into

three groups as shown in the table. Within each of these groups the observed number of recurrences and salvage hormonal therapies in the validation dataset is shown, as well as the calculated Kaplan-Meier estimate of the three year recurrence or hormonal therapy probability. The results show that a larger proportion of recurrences in the groups with the higher predicted probability, this provides support for the validity of the model. It is also clear that the model is predicting a slightly greater proportion of recurrences than were actually observed, however if one includes hormonal therapy, then the prediction are close to the observed data.

4 Discussion

In this paper we present the results of fitting a complex statistical model to PSA and clinical recurrence data following radiation therapy, and then show how this model can be used for individual monitoring of a patient's disease progression. The model predicts, based upon baseline clinical features, as well as all post-treatment PSA values, the probability of future clinical recurrences with and without the use of hormonal therapy, and predicts future PSA values. After potential further enhancements and validation we hope to be able to make the program available for others to use through a web-based interface, for practical post treatment clinical predictive use.

As with any model it contains a number of assumptions. We cannot hope to incorporate in the model all aspects of the known biology of prostate cancer progression, and in this sense it is too simple. However, compared to most statistical models this one would be regarded as complex, but this level of complexity was considered necessary to capture the variability in disease progression. An assessment of whether the assumptions are justified can be made empirically, by considering whether the model fits the current data, whether it can be validated using new data and whether the parameter estimates are plausible. On all three counts the model appears to be adequate.

One of the clearest findings from the parameter estimates is the strength of the association of the slope of PSA with the hazard of clinical recurrence. This is consistent with the well known observation that PSA doubling time is an important determinant of disease progression (Hanks

et al 1993, Sartor et al 1997, D'Amico et al 2003). Another substantive finding is that baseline variables, such as Gleason and PSA retain some information about disease recurrence even when the current value and slope of PSA are known.

The major contribution of this paper is intended to be the illustration of the ability to predict future disease progression. We provide estimates and uncertainty ranges for these predictions. We believe that such quantitative information will enhance rational decision making concerning actions to take. Possible actions might include initiation of hormone therapy or return for next PSA measurement at a shorter than or longer than usual interval.

Another possible use for this model is as a method for defining biochemical recurrence. For example, one could define a patient as having biochemical recurrence if the estimated probability of clinical recurrence within 3 years is greater than 30% say. We note that such a definition utilizes all the serial PSA and baseline data for the patient, not just the last four PSA values as in the ASTRO definition.

We are not the first to develop statistical models to utilize a series of biomarker values for early detection of disease or monitoring disease progression. Other examples are using CA125 for early detection of ovarian cancer (Skates et al 2001), using PSA for early detection of prostate cancer (Slate and Cronin 1997), and using PSA for detecting disease recurrence in prostate cancer (Pauler and Finkelstein 2002). A key feature of all these publications is that the whole series of biomarker values is utilized and that they can handle unequally spaced observations, this is in contrast to simple methods which require the biomarker to be above a certain cut-off or ad-hoc methods, such as the ASTRO definition which do not adapt well to heterogeneity in the time interval between measurements.

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Table 1: Odds-ratio estimates from cure model.

Parameter	odds-ratio	95% interval
$I(Tstage = 1)$	0.19	(0.08,0.46)*
$I(Tstage = 2)$	0.22	(0.09,0.52)*
$I(Tstage = 3 - 4)$	1.00	
ln(1+basePSA)	2.66	(1.83,3.86)*
Gleason	1.18	(0.98,1.42)
Age at RT (yrs)	0.99	(0.96,1.02)
Total Dose (Gy)	0.89	(0.83,0.96)*
Duration (days)	0.97	(0.93,1.02)

* indicates 95% interval excludes 1.0

Table 2: Relative hazard estimates from clinical recurrence model.

Parameter	Relative hazard	95% interval
$I(Tstage = 1)$	0.46	(0.23,0.90)*
$I(Tstage = 2)$	0.83	(0.52, 1.34)
$I(Tstage = 3 - 4)$	1.00	
ln(1+basePSA)	1.32	(1.04,1.66)*
Gleason	1.21	(1.04,1.41)*
Total Dose (Gy)	1.05	(0.99,1.12)
Current PSA[1]	1.11	(0.98,1.25)
Current PSA Slope[2]	691	(156,3047)*
Hormonal Therapy	0.056	(0.02,0.20)*

* indicates 95% interval excludes 1.0.
[1] $\ln(1 + PSA)$.
[2] square root(slope of $\ln(1 + PSA)$).

Table 3: Validation of the longitudinal model for predicting future PSA values. Comparison of model predicted PSA ranges and observed PSA data from the validation dataset.

	0-1 Year	1-2 Years	2-3 Years
Total #PSA measurements	287	406	306
Percentage > upper 97.5%	1%	3.6%	3.9%
Percentage between 2.5% and 97.5%	95.5%	92.8%	91.2%
Percentage < lower 2.5%	3.5%	3.6%	4.9%

Table 4: Validation of the survival model for predicting clinical recurrences. Comparison of model predicted and observed recurrences within 3 years.

Prob. of recur in 0-3 yrs	No. patients	No. recur	No. recur or HT	3yr KM estimate of recur or HT
0.00-0.02	191	0 (0.0%)	4 (2.1%)	0.02
0.02-0.10	257	5 (2.0%)	8 (3.1%)	0.04
0.10-1.00	93	6 (6.5%)	12 (12.9%)	0.18

Figure 1: Individual prediction of distribution of time to clinical recurrence (up to 4 years) for 3 selected censored patients with long follow-up. The left-side vertical axis is shown on a log(PSA+1) transformed scale. The vertical line indicates the time of last contact. The right-side vertical axis shows the probability of being recurrence free from the date of last contact. The right hand graph shows uncertainty estimates of the predictions.

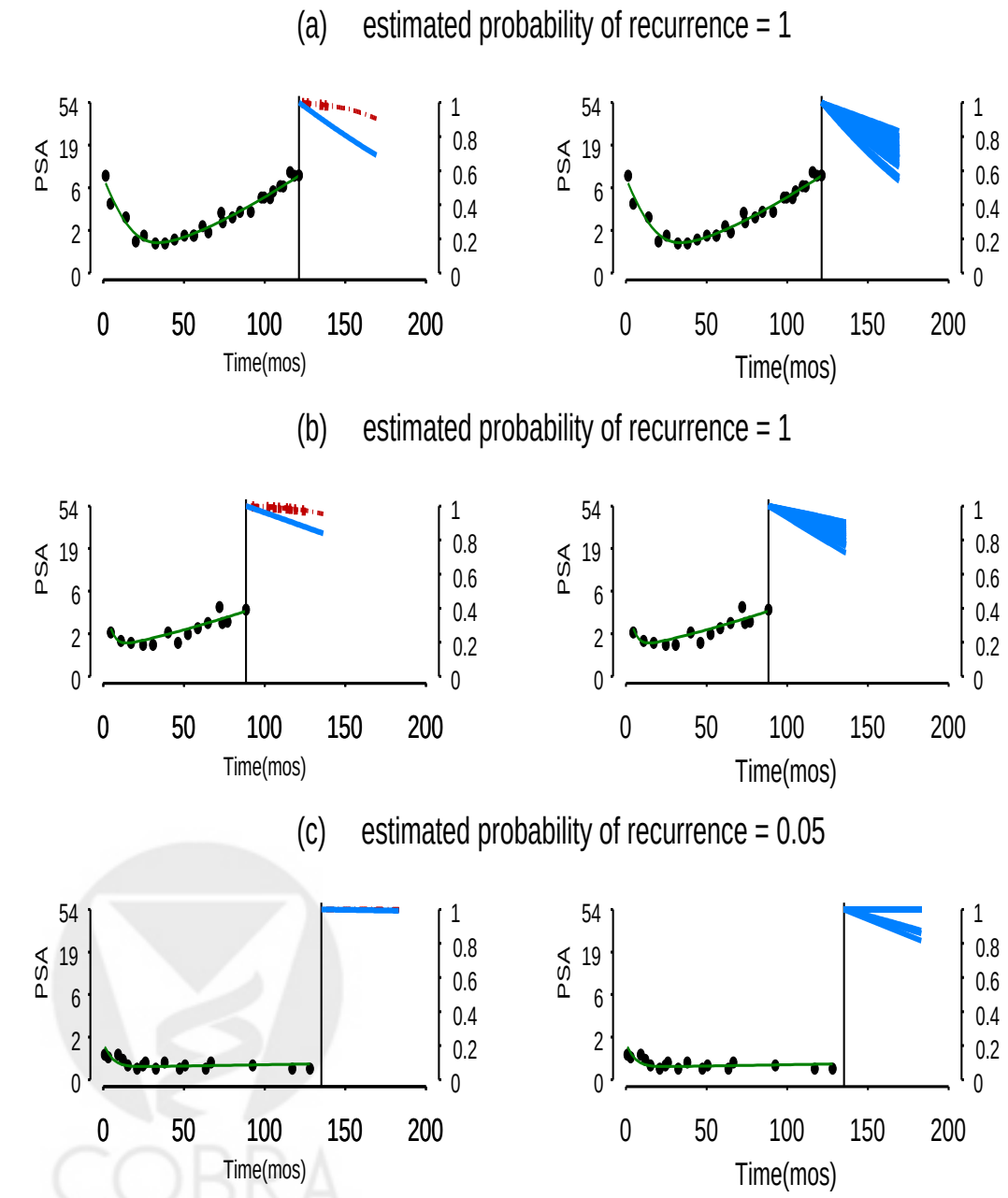


Figure 2: Individual prediction of distribution of time to clinical recurrence (up to 4 years) for 3 selected censored patients with short follow-up. The left-side vertical axis is shown on a log(PSA+1) transformed scale. The vertical line indicates the time of last contact. The right-side vertical axis shows the probability of being recurrence free from the date of last contact. The right hand graph shows uncertainty estimates of the predictions.

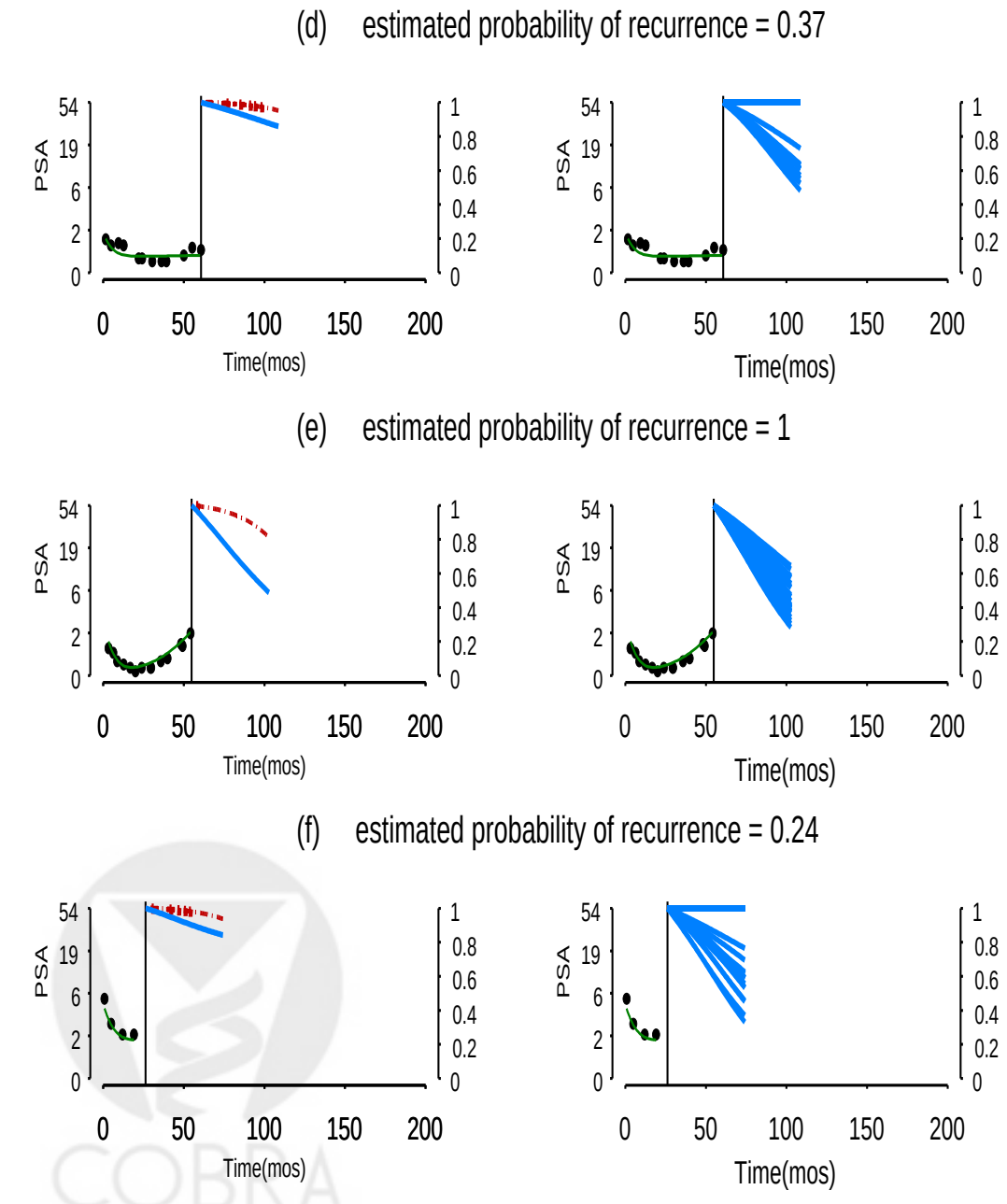
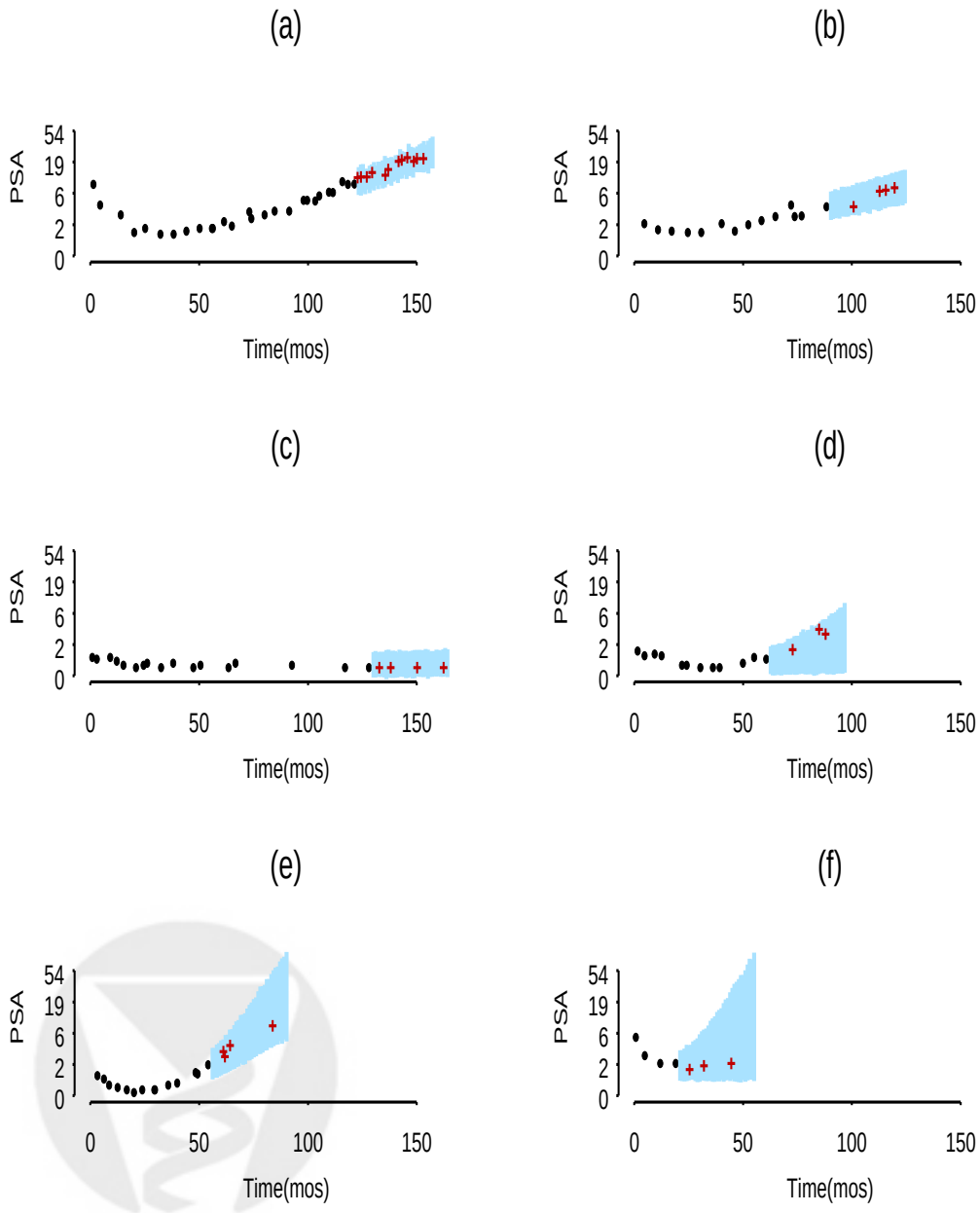


Figure 3: Validation of the model. Comparison of future observed PSA values with predicted PSA 95% ranges (shaded region) derived from statistical model for 6 selected patients.



5 Appendix

The statistical model has three components, one to model the possibility of cure, one to model the serial PSA measurements and one to model the hazard of a clinical event. The data available on patient i is $(PSA_i(U_1), PSA_i(U_2), ..., PSA_i(U_m), X_i, t_i, \delta_i)$ where $PSA_i(U_1)$ is the value of PSA at time U_1, X_i are baseline covariates, t_i is the time of clinical recurrence or last follow-up and δ_i is the indicator for clinical recurrence. A logistic regression model was used for the probability of cure. Let D_i be the latent cure indicator, with $D_i = 1$ denoting cure and $D_i = 2$ denoting not cure. Thus each patient is in one of two categories, either they are susceptible to recurrence or non-susceptible to recurrence. The value of D_i is unknown except for patients who have had clinical recurrence. It is reasonable to assume that D_i only depends on baseline and treatment variables, thus we assume $log(P(D_i = 1)/(1 - P(D_i = 1))) = \beta_0 + \sum X_{ij}\beta_j$. Non-linear hierarchical mixed models were used for serial PSA measurements. Let $log(1 + PSA_i(t_{ij})) = R_i(t_{ij}) + e_{ij} = log(1 + Z_i(t_{ij})) + e_{ij}$ where e_{ij} is measurement error, which we assume has a student's T distribution with 5 degrees of freedom. The longitudinal model for PSA is $Z_i(t) = a_i exp(-b_i t) + c_i exp(d_i t)$. For cured patients we assume d_i is close to zero. The set (a_i, b_i, c_i, d_i) are latent variable random effects, which have their own joint multivariate normal distribution for each value of D_i, and are restricted to be positive, they are also allowed to depend on baseline covariates, through a regression model. The proportional hazards model for a clinical event for susceptible patients $(D_i = 2)$ is given by $\lambda_0(t)exp(\alpha_1 R_i(t) + \alpha_2 sl_i(t) + \kappa HT(t - \tau_i) + \omega X_i)$. In this model $sl_i(t)$ is the square root of the slope of $R_i(t)$, and $HT(t)$ is a function which is non-zero on 0 to 60 months, it linearly decreases from one at t=0 to zero at t=60, and τ_i is the initiation time of hormonal therapy for those who received it.

PSA data after hormonal therapy is not used in fitting the model, but clinical recurences after hormonal therapy are used. The model is fit using Markov Chain Monte Carlo (MCMC) methods, as described in Yu et al (2003). The MCMC gives the posterior distribution of all the parameters and the latent variables.

The prediction of a future PSA value for patient i at time t is given by the formula $PSA_i(t) = exp(log(1 + Z_i(t)) + e) - 1$, where $Z_i(t) = a_i exp(-b_i t) + c_i exp(d_i t)$, with (a_i, b_i, c_i, d_i) produced by the MCMC method and e is a random draw from a T_5 distribution. Consecutive iterates of the MCMC give different values of the parameters and hence of $PSA_i(t)$, thus giving a range of possible future PSA values. We use 2000 draws from the MCMC and present the 2.5th to 97.5th percentile range.

For the prediction of future clinical events the probability that patient i is event free T months into the future can be calculated from the equations describing the model. Different iterates from the MCMC will give different probability, both the average probability and the range of probabilities (from 40 draws) are presented graphically.

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