Prognostication of metastatic death in uveal melanoma patients: a Markov multi-state model.

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# **ABSTRACT**

## **Background/Aims**

Uveal melanoma is fatal in almost 50% of patients. We previously developed a prognostic model to predict all-cause mortality. The aim of this study was to improve our model by predicting metastatic death as a cause-specific event distinct from other causes of death.

## **Methods**

Patients treated in Liverpool were included if they resided in England, Scotland or Wales and if their uveal melanoma involved the choroid. They were flagged at the National Health Service Cancer Registry, which automatically informed us of the date and cause of death of any deceased patients. A semiparametric Markov multi-state model was fitted. Two different baseline hazard rates were assumed, with state transition-specific covariates. For both failure types, age at treatment and sex were used. For the metastatic death case, these factors were added: anterior margin position, largest basal tumour diameter, tumour thickness, extra-ocular extension, presence of epithelioid melanoma cells, presence of closed connective tissue loops, increased mitotic count, chromosome 3 loss, and chromosome 8q gain. Missing data required a multiple-imputation procedure.

## **Results**

The cohort comprised 4161 patients, 893 of whom died of metastastic disease with another 772 dying of other causes. The bootstrapped C-index for metastatic death prediction was 0.86, denoting very good discriminative performance. Bootstrapped calibration curves at two and five years also showed very good performance.

## **Conclusions**

Our improved model provides reliable, personalised metastatic death prognostication using clinical, histological and genetic information, and it can be used as a decision support tool to individualize patient care in a clinical environment.

# **INTRODUCTION**

Hepatic metastases are the primary cause of death in patients with uveal melanoma; however, tumour dissemination is only rarely detectable at the time of primary ocular treatment. There is a need for prognostic tools to estimate the risk of metastatic death and to predict when this might happen. If sufficiently reliable, such tools would enable medical care to be personalized, so that patients with a low risk of metastasis can be reassured while targeting special measures, such as counselling and systemic surveillance, at those who are likely to succumb to their disease. Since many patients with uveal melanoma are elderly, estimation of time to metastasis helps to predict whether death is likely to be caused by their uveal melanoma or by unrelated disease(s).

We previously developed a prognostic tool that estimated all-cause mortality; however, such an endpoint is not ideal because the cause of death is not usually difficult to ascertain, because death from unrelated disease is common, and because treatment or disease-related factors do not increase the risk of death from other causes. [Kroll] The aim of the present study, therefore, was to improve our prognostic tool by using metastatic death as the endpoint.

# **MATERIALS AND METHODS**

## ***The data***

The model was developed with data from 4161 patients treated for uveal melanoma at the Liverpool Ocular Oncology Centre. Patients were included in the study if they resided in England, Scotland or Wales, and if their tumour involved the choroid. Diagnosis was based on clinical findings and, if these were inconclusive, on morphological examination of a biopsy. Tumour location and intraocular spread were determined by ophthalmoscopy and slit-lamp examination. Tumour dimensions were measured by ultrasonography, which was also used to detect extraocular spread. High-grade malignancy was recognized histologically by noting epithelioid melanoma cells, closed connective tissue loops and increased number of mitoses in the tumour. Tumours having increased metastatic potential were identified using molecular pathology techniques to detect chromosome 3 loss, chromosome 8q gain, and, recently, by using immunohistochemistry to determine loss of nuclear BAP1 protein expression.

Most patients were treated by plaque brachytherapy, proton beam radiotherapy, local resection and phototherapy, or a combination of these modalities. When such methods were considered unlikely to succeed the eye was removed. Patients considered to have a high risk of metastatic disease were referred to an oncologist for long-term surveillance, which consisted of liver ultrasonography or, preferably, magnetic resonance imaging. Metastatic disease, which almost always involved the liver, was treated with various forms of chemotherapy or immunotherapy or, in rare cases, by partial hepatectomy. There is some evidence of prolongation of life if hepatic metastases are detected by six-months MRI scans [Marshall].

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| **Table 1 Descriptive statistics** | | | | | |
| **Variable** | **Count** | **Mean** | **Median** | **Range** | **Number missing** |
| Event time | 893: metastases  772: other causes  2496: censored | - | - | [0.019, 33.64]  [0.0055, 36.95]  [0.0055, 37.45] | - |
| Age at treatment (years) | 4161 | 61.38 | 62.45 | [12.35, 98.18] | - |
| Sex | 2142: males  2019: females | - | - | - | - |
| Largest tumour diameter from ultrasound (mm) | 4051 | 12.41 | 12.41 | [1.20, 28] | 110 |
| Anterior margin | 1103: pre-ora  3057: post-ora | - | - | - | 1 |
| Extra-ocular extension | 275: yes  3886: no | - | - | - | - |
| Tumour height from ultrasound (mm) | 4063 | 5.38 | 5.00 | [0, 20] | 98 |
| Tumour cell type | 1270: epitheliod/mixed  917: spindle | - | - | - | 1974 |
| Presence of closed connective tissue loops | 598: yes  600: no | - | - | - | 2963 |
| Mitotic count per 40 high power fields | 674: 0-1  414: 2-3  366: 4-7  308: 7+ | - | 2-3 | - | 2399 |
| Chromosome 3 loss | 269: yes  333: no | - | - | - | 3559 |
| Chromosome 8q gain | 272: yes  330: no | - | - | - | 3559 |

## **The model**

A semiparametric Cox model with two strata was fitted [Therneau][Putter], using the data shown in Table 1. The strata represent metastatic death and death from unrelated causes. These two strata both depend on sex and age at primary ocular treatment. Additional covariates are specific to the hazard rate of metastatic death, namely: anterior margin position, largest basal tumour diameter, tumour thickness, extra-ocular extension, tumour cell type, presence of closed connective tissue loops, increased mitotic count, chromosome 3 loss, and chromosome 8q gain.

Once the hazard rates’ parameters were fitted, the Breslow estimator of the cumulative cause-specific hazard was computed and then used to estimate the cumulative probability of metastatic death [Aalen][Putter].

Values for missing data were estimated using the Bayesian Alternating Conditional Expectations algorithm [Harrell]. Essentially, this estimated each of the missing variables as a function of the other variables. For example, if mitotic count and chromosome 3 loss were not known, these were estimated by modelling their relationships with all the other available (not missing) variables. This process approximated the joint distribution of the baseline variables. Ten different data sets were sampled from the estimated joint distribution, and ten models were fitted, one for each imputed data set.

The statistics of the final model were “corrected” for the inherent uncertainty of the multiple imputation procedure, represented by the variability of the imputed values, and the correlations amongst the imputed data sets [Appendix]. These corrections resulted in inflated uncertainty in the final model parameters estimates, thereby producing conservative estimates of the test statistics, which would otherwise have been excessively optimistic. The final aim was to reduce the chance of a false discovery resulting from falsely rejecting the null hypothesis of no effects of a covariate on survival estimates.

We calculated two validation measures of accuracy: discrimination and calibration [Harrell]. Discrimination described the ability of the model to rank the outcomes as a function of the prognostic factors. It was expressed in terms of the C-index, which determines the diagnostic power of a test applied to censored data. Calibration described the precision of the predictions compared with actuarial outcome for different risk groups. Both measures of accuracy are appropriate with censored data. The 95% Confidence limits for accuracy were calculated by bootstrapping.

# **RESULTS**

Figure 1 shows the cumulative incidence functions of metastatic death versus death from other causes. The curves show that the probability of metastatic death exceeds the probability of death from unrelated disease up to about 18 years post treatment; from this point onward, the latter predominates.



In Table 2, we report the averaged coefficients (over the ten fitted models) for the two causes of death, with p-values and odds ratios (and attendant confidence intervals.) The p-values and odds ratios confidence intervals were corrected for the imputation process. The relatively wide odds ratio confidence intervals for the histologic and genetic covariates reflect the high rate of missing data.

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| Table 2 Model parameters and statistics | | | | |
| **Covariate** | **Cause of death** | **Coefficient** | **p-value** | **Odds Ratio [95% C.I.]** |
| Age at treatment | Other | 0.0887 | <0.00001 | 1.093 [1.0848, 1.101] |
| Sex | Other | 0.262 | 0.000770 | 1.299 [1.116, 1.514] |
| Age at treatment | Metastasis | 0.00626 | 0.0932 | 1.006 [0.999, 1.014] |
| Sex | Metastasis | 0.0495 | 0.557 | 1.051 [0.891, 1.240] |
| Tumour diameter | Metastasis | 0.0971 | <0.00001 | 1.102 [1.0612, 1.144] |
| Anterior margin | Metastasis | 0.252 | 0.0156 | 1.287 [1.0490, 1.579] |
| Extra-ocular extension | Metastasis | 0.419 | 0.000255 | 1.521 [1.215, 1.903] |
| Tumour thickness | Metastasis | 0.0360 | 0.0138 | 1.037 [1.0074, 1.067] |
| Epithelioid melanoma cells | Metastasis | 0.478 | 0.00231 | 1.614 [1.186, 2.195] |
| Closed-loops | Metastasis | 0.406 | 0.00285 | 1.500 [1.149, 1.958] |
| Mitotic count/40 high-power fields | Metastasis | 0.249 | 0.0000338 | 1.282 [1.140, 1.442] |
| Chromosome 3 loss | Metastasis | 1.436 | 0.0000133 | 4.202 [2.202, 8.019] |
| Chromosome 8q gain | Metastasis | 0.47 | 0.0382 | 1.601 [1.026, 2.497] |

The bootstrapped C-index for metastatic death survival prediction (with 95% confidence interval) was 0.86 [0.84, 0.88]. In Fig. 2 and Fig. 3 we report the bootstrapped accuracy calibration curves (with 95% confidence intervals) for metastatic death survival prediction at two and five years, respectively. The light-grey line, denoting the theoretical perfect performance, is fully enclosed within the confidence limits, indicating good accuracy.

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# **DISCUSSION**

The C-index and the calibration curves indicate that our model provides reliable, personalised metastatic death prognostication.

The main strengths of our study are the large number of patients, the abundant genetic and histological data, the long follow-up and the accurate reporting mortality. The main weakness is the missing histological and genetic data in a significant proportion of patients. This is because methods for genetic analysis of small tumours samples and techniques for biopsy of tumours treated with radiotherapy were developed relatively late in the course of this study (i.e., approximately 2007). Furthermore, not every patient chose to undergo a prognostic biopsy or analysis of the tumour following enucleation or surgical resection.

The model can be used even when a subset of the full covariates set is missing [Harrell]. Our model addresses the problem of missing covariates by using the method of projections, that is, by fitting a model with the reduced covariates set to the outputs of the full model. This reduced model then provides as good an approximation as possible to the full model. This method is computationally simple, and has the advantage of allowing “honest” confidence intervals estimates on the predictions of the reduced model since the uncertainties in the original full model can be carried over to the reduced model. This is conceptually different from fitting a new, smaller model to the original data, which would not be a valid inferential strategy since we already fitted a more complex model to the data [Harrell].

Most studies report cancer-related mortality using Kaplan-Meier analysis; however, this method censors the patients who die of unrelated diseases. This wrongly assumes that patients do not die from other causes, which results in cancer mortality being overestimated [Aalen]. This problem of ‘competing risks’ can be overcome by considering the cumulative cause-specific mortality or cumulative incidence [Aalen]. Studies on cause-specific uveal melanoma mortality have mostly focused on either univariate analysis of survival based on the cumulative incidence method, or competing risks proportional hazards regression based on Fine and Grey’s estimator [Kujala][Kroll][Fine]. While the latter method avoids the highly nonlinear effects of covariates on the cumulative incidence function, it may result in false predictions. This is because it assumes that patients dying of unrelated disease remain in the risk set [Putter]. In any case, nonlinearities are not a major concern when only the final output of the model is of interest [Andersen]. For these reasons, we modelled the cause-specific uveal melanoma mortality rate and unrelated mortality using semiparametric Cox models, then formulating the problem of predicting cumulative incidences as a special case of a Markov multi-state model [Andersen][Aalen][Putter].

With regards to future research, we anticipate that as our dataset expands we will be able to incorporate into our models a larger number of predictors, such as aberrations of BAP1, EIF1AX, SF3B1 and other genes. There is also a need for our model to be validated externally and a multicentre study is already in progress to achieve this aim, under the auspices of the European Ophthalmic Oncology Group.

As for the clinical implications, more reliable prognostication should enable physicians to reassure patients more confidently when counselling those having only a small risk of metastasis. Better prediction of metastatic disease should make it possible for liver imaging, systemic adjuvant therapy and other procedures to be targeted more accurately at high-risk individuals. There is scope for further research into the impact of such measures on quality of life, physical health and survival.

In conclusion, we have improved our model for predicting survival after treatment for uveal melanoma and hope this will enhance the care that is provided to patients with this disease.

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