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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 metastatic disease with another 772 dying of other causes. The optimism-corrected, 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.

1. 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, the Liverpool Uveal Melanoma Prognosticator Online (LUMPO) model, that estimates all-cause mortality [1]; however, such an endpoint is not ideal for the following reasons: the cause of death is not usually difficult to ascertain; death from unrelated disease or age is common; and treatment or disease-related factors do not increase the risk of death from other causes

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[2].

The aim of the present study, therefore, was to develop a prognostic model of metastatic death.

2. Materials and methods

2.1. 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. Uveal melanomas having increased metastatic potential were also identified using molecular pathology techniques demonstrating chromosome 3 loss and chromosome 8q gain, as well as more recently, by using immunohistochemistry to determine loss of nuclear BAP1 protein expression [3]. See Table 1 for summary statistics.

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 [4].

2.2. The model

A semiparametric Cox model with two strata was fitted [5,6], 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 [6,7] (see Eq. (A.10)).

Values for missing data were estimated using the Alternating Conditional Expectations algorithm coupled with an approximate Bayesian bootstrap [8]. Essentially, this method estimates from the bootstrap samples each of the missing variables as a semi-parametric 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. The bootstrap process approximates the joint distribution of the baseline variables. Ten different complete data sets were sampled from the estimated joint distribution (after a burn-in period of twenty samples), and ten models were fitted, one for each imputed data set. Table 2 shows the adjusted R^2 achieved in predicting the missing variables. It's interesting to see that despite the high rate of missing entries, variables like "chromosome 3 loss" and "chromosome 8 gain" can be predicted reasonably well. The predictive performances are in line with the expected performances of multiple imputation procedures [8].

The statistics of the final model were "corrected" for the inherent uncertainty of the multiple imputation procedure, represented by the variances of the models fitted on the imputed data sets, and the correlations amongst the models across the imputed data sets (see Eq. (A.11) for details). 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 [8]. Discrimination described the ability of the model to

Table 1
Descriptive statistics of outcomes and covariates. For discrete variables, counts are reported for each level of the factor. For continuous variables, mean, median and range [minimum, maximum] are reported. The number of missing entries is reported, if any.

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