Estimating prognosis for survival after treatment of choroidal melanoma

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Abstract

Choroidal melanoma is fatal in about 50% of patients. This is because of metastatic disease, which usually involves the liver. Kaplan–Meier survival curves based only on tumor size and extent do not give a true indication of prognosis. This is because the survival prognosis of choroidal melanoma correlates not only with clinical stage but also with histlogic grade, genetic type, and competing causes of death. We have developed an online tool that predicts survival using all these data also taking normal life-expectancy into account. The estimated prognosis is accurate enough to be relevant to individual patients. Such personalized prognostication improves the well-being of patients having an excellent survival probability, not least because it spares them from unnecessary screening tests. Such screening can be targeted at high-risk patients, so that metastases are detected sooner, thereby enhancing any opportunities for treatment. Concerns about psychological harm have proved exaggerated. At least in Britain, patients want to know their prognosis, even if this is poor. The ability to select patients with high risk of metastasis improves prospects for randomised studies evaluating systemic adjuvant therapy aimed at preventing or delaying metastatic disease. Furthermore, categorization of tissue samples according to metastasis improves prospects for randomised studies evaluating systemic adjuvant therapy aimed at preventing or delaying metastatic disease. Furthermore, categorization of tissue samples according to metastasis improves prospects for randomised studies evaluating systemic adjuvant therapy aimed at preventing or delaying metastatic disease. Furthermore, categorization of tissue samples according to metastasis improves prospects for randomised studies evaluating systemic adjuvant therapy aimed at preventing or delaying metastatic disease. Furthermore, categorization of tissue samples according to metastasis improves prospects for randomised studies evaluating systemic adjuvant therapy aimed at preventing or delaying metastatic disease. Furthermore, categorization of tissue samples according to metastasis improves prospects for randomised studies evaluating systemic adjuvant therapy aimed at preventing or delaying metastatic disease.

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1. Introduction

Approximately 90% of all intraocular melanomas involve the choroid, the remainder being confined to iris and ciliary body. Most patients present with visual symptoms, such as blurred vision (Damato, 2001). If neglected, these uveal tumors can cause visual loss, a painful and unsightly eye, and death from intracranial spread or metastatic disease. Such metastatic disease almost always involves the liver and is only rarely detectable at the time of ocular treatment.

It is widely stated that patients with uveal melanoma have a 50-50 chance of dying of their disease. Although this summary statistic holds true when applied to all patients, it is mostly false when applied to individuals. This is because in most patients the prognosis is actually very much better or considerably worse than this estimate. An important aim of this article is, therefore, to explain how the accuracy of prognostication can be enhanced to the level at which it is relevant to individual patients.

Most cancer prognostication is based on the TNM (tumor, node, metastasis) staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). The TNM staging of uveal melanomas has recently been improved, and we have contributed significantly to this project (Finger, 2009). The TNM staging system currently uses only clinical data. Can it be enhanced by taking account of histologic and genetic predictors if so, how? In this review we discuss a possible way forward.

Survival after treatment of cancer tends to be displayed using Kaplan–Meier analysis, but is this methodology satisfactory? We have developed an online tool that provides a better impression of disease-free survival after treatment of choroidal melanoma and in this article we present our approach.

Treatment of metastatic disease is only rarely effective, and doubts have been expressed regarding the value of screening and treatment (Augsburger et al., 2009; Kim et al., 2010). However, some recent results are encouraging (Sato, 2010). Is prognostication significantly improved when diameter and other predictors are taken into account (Finger, 2009). In our multivariate analyses, thickness does not appear to be a significant independent risk factor when diameter and other predictors are taken into account (Damato and Coupland, 2009). Thickness is influenced not only by neoplastic growth but also by tumor prolapse into sub-retinal space, and interstitial edema.

2. Survival predictors

2.1. Clinical risk factors

2.1.1. Age and sex

It has been suggested that older age and male gender correlate with reduced survival (Seddon et al., 1983; Virgili et al., 2008). However, it is uncertain as to what extent these correlations are the result of bias arising from competing risks (i.e., death from other causes) (Kujala et al., 2003).

2.1.2. Tumor dimensions

Numerous studies have shown a strong correlation between largest basal tumor diameter and reduced survival probability (Damato and Coupland, 2009). One explanation for this association is that large tumors have been present for a longer time and have, therefore, had more opportunity to develop metastatic capability and disseminate. This hypothesis assumes that metastatic spread tends to start after the tumor has grown large. The same correlation is partly explained by the likelihood that a large uveal melanoma has been metastasising for a longer period so that any metastases have also been growing for a longer time (i.e., ‘lead-time bias’).

Another possibility is that metastatic spread commences early, when the tumor size is still small, so that large tumor size is mostly an indicator of increased tumor malignancy and greater growth rate. Many patients with uveal melanoma experience long delays before treatment (Ah-Fat and Damato, 1998). In such cases, the more malignant melanomas are likely to grow more than those that are small metastatic potential. Our view is that all these explanations are equally plausible and that different mechanisms apply to different tumors according to whether they start to metastasise before or after they grow large.

Greater tumor thickness is associated with higher metastatic mortality and some consider this to be an important survival predictor (Shields et al., 2009). Tumor thickness is one of the factors used to estimate survival with the TNM uveal melanoma staging system (see 2.1.5) (Finger, 2009). In our multivariate analyses, thickness does not appear to be a significant independent risk factor when diameter and other predictors are taken into account (Damato and Coupland, 2009). Thickness is influenced not only by neoplastic growth but also by tumor prolapse into sub-retinal space, and interstitial edema.

2.1.3. Ciliary body involvement

Several studies show that ciliary body involvement is associated with a poorer prognosis for survival (Seddon et al., 1983). The explanation for this correlation is uncertain. Large uveal melanomas are more likely to involve ciliary body (Damato and
Furthermore, they more likely to show adverse histological and genetic risk factors (Damato et al., 2007).

2.1.4. Extraocular spread

Extraocular spread is associated with increased mortality (Coupland et al., 2008). In our analysis of 847 eyes enucleated for uveal melanoma and assessed at our hospital, we found extraocular spread to correlate significantly with other adverse, clinical, histological and genetic risk factors for metastasis (Coupland et al., 2008). Whether extraocular extension contributes to metastatic risk or whether it is only an indicator of increased tumor malignancy is uncertain.

2.1.5. TNM staging system

The 7th TNM staging system categorises tumors according to their size, categorized by tumor basal diameter and height, also taking account of ciliary body involvement and extraocular spread (i.e., nil, <5.1 mm and >5.0 mm). Risk of metastatic death is estimated according to: ocular tumor stage (with categories having the same prognosis grouped into the same stage); regional lymph node involvement; and presence of known metastases (Finger, 2009).

2.2. Histological risk factors

2.2.1. Melanoma cytomorphology

The presence of epithelioid melanoma cells is associated with a worse prognosis (Fig. 1a and b) (McLean et al., 1978). Differentiation between spindle and epithelioid cells is subjective and, furthermore, there is no consensus at present as to how many cells need to show an epithelioid cytomorphology for the tumor to be categorised as ‘mixed’ or ‘epithelioid’. Nucleolar size, specifically the mean of the ten largest nucleoli (MLN) also correlates with increased mortality and is widely used as a prognostic indicator (Al Jamal et al., 2003). Nucleolar assessment is facilitated by methods such as silver-staining.

2.2.2. Extravascular matrix patterns

In 1993, Folberg et al. described nine patterns of what they then considered to be blood vessels, but which were subsequently found to lack endothelial cells (i.e., ‘vasculogenic mimicry’) (Lin et al., 2005; Folberg et al., 1993). Metastatic death correlates most strongly with the presence of at least three, back-to-back, closed loops (i.e., ‘networks’). These patterns are best appreciated by light microscopy on sections stained with the periodic acid Schiff (PAS) reagent, without hematoxylin counter-staining (Fig. 1c). We and others have confirmed that PAS-positive networks correlate with other risk factors for metastasis and with increased mortality (Coupland et al., 2008; Damato et al., 2007).

2.2.3. Microvascular density

The microvascular density (MVD) is measured by counting the number of blood vessels per unit area in the most vascularised parts of the tumor (‘hot spots’), using anti-endothelial antibodies to identify these vessels (e.g., anti-CD34 antibodies). MVD is higher in tumors with epithelioid cells, high-risk extravascular matrix patterns, and increased mortality (Mäkitie et al., 1999).

2.2.4. Non-neoplastic cellular infiltrates

Macrophages are commonly present in uveal melanomas and their identification is facilitated by immunohistochemistry, using the anti-CD68 antibody, after melanin bleaching. The number of macrophages is higher in tumors with epithelioid cells, increased microvascular density and large size as well as in tumors that have proved fatal (Mäkitie et al., 2001b). This is possibly because...
macrophages are involved in angiogenesis and because they may suppress anti-tumor immune responses (Jager et al., 2011). Tumor-infiltrating lymphocytes (TILs), particularly T-lymphocytes, are also associated with increased metastatic mortality (Whelchel et al., 1993). Increased HLA classes I and II expression, as determined by immunohistochemistry, is associated with poor survival and it has been suggested that such expression suppresses immune responses to the tumor (Ericsson et al., 2001; Maat et al., 2009).

2.2.5. Cell proliferation

There are several indicators of cell proliferation. The mitotic count per specified number of high-power fields is widely accepted and correlates strongly with risk of metastatic death (Coupland et al., 2008; Damato et al., 2007). In sections stained with hematoxylin and eosin, however, it can be difficult to recognise mitotic figures or to differentiate them from occasional apoptotic bodies. Dividing cells can be identified with antibodies such as PHH3 (also known as Ser-10) (Fig. 1d) (Angi et al., 2009). However, staining with this antibody fades over time and is used only in a few centers. Other markers such as Ki-67 and PC-10 are more widely used and have been shown to correlate with other predictors of metastasis and with increased mortality (Al-Jamal and Kivelä, 2006; Seregard et al., 1998). There is no uniform way of counting positive cells and for preparing specimens so that results from different centers vary considerably.

2.3. Genetic

2.3.1. Chromosome 3 loss

In 1996, Prescher et al. correlated chromosome 3 loss (i.e., ‘monosomy 3’) with metastatic death (Prescher et al., 1996). Fatality occurred exclusively in patients with monosomy 3 and almost all patients with this abnormality died by the end of the study. Others have confirmed these findings using a variety of methods (Damato et al., 2007; Damato et al., 2010; Shields et al., 2011; Trolet et al., 2009; Young et al., 2007). Fatality can occur also with partial chromosome deletions, which can be missed with methods such as FISH (Damato et al., 2007) (Fig. 2H). Higher-resolution techniques are therefore replacing FISH. Our current approach is to perform multiplex ligation-dependent probe amplification (MLPA) in the first instance (Fig. 3) (Damato et al., 2010). In selected cases, we perform additional: (a) a CGH for tumors with apparent disomy 3 with high-grade histological malignancy; and (b) microsatellite analysis (MSA) when the DNA concentration of the sample is too small for MLPA or when MLPA results are inconclusive. We hope to be able to compare our techniques with gene expression profiling (GEP) (see 2.3.5).

Apart from inadequate tumor sample cellularity, there are other causes of failure, such as isodisomy 3, in which both copies of the same chromosome are from the same parent. Furthermore, uveal melanomas can show considerable genetic intra-tumor heterogeneity (Dopierała et al., 2010). This has given rise to concerns about sampling error. Further studies are required to determine whether prognostication relying on tumor biopsies is as reliable as that based on large samples obtained from local resection and enucleation specimens. Recent studies have proposed a critical area of chromosome 3 loss (e.g. BAP1); these results require independent validation but suggest that that sensitivity for prognostication in uveal melanoma is likely to improve in future (Harbour et al., 2010).

2.3.2. Chromosome 8 gain

This abnormality can arise as a result of abnormal splitting of the chromosome during cell division. Instead of the two chromatids moving to different cells, both short arms of chromosome 8 move to one cell with both long arms of the same chromosome going to the other, producing ‘isochromosome 8q’. Another mechanism is trisomy 8 formation. Gains of chromosome 8q correlate with increased mortality (Fig. 2G). White et al. have suggested that chromosomes 3 loss and 8q gain must be present together for metastatic disease to occur (White et al., 1998). Using MLPA, we have found that metastatic death can rarely occur with monosomy 3 alone (Damato et al., 2010) (Fig. 3); however, further studies using more sensitive tests are needed to determine whether in these fatal cases chromosome 8q gains are indeed absent or merely undetected.

2.3.3. Chromosome 6p gain

Chromosome 6p gain tends to arise as a result of isochromosome 6p. It is associated with a relatively good prognosis (Parrella et al., 1999). This is because monosomy 3 is less common in tumors with chromosome 6p gain (Damato et al., 2010). Furthermore, when both these abnormalities occur together, survival is better than with monosomy 3 alone (Damato et al., 2010).

2.3.4. Chromosome 1p loss

Chromosome 1p loss correlates with chromosome 3 loss and increased mortality (Damato et al., 2010; Kilic et al., 2005). However, it loses significance in our multivariate analyses.

2.3.5. Gene expression profiling

Uveal melanomas cluster into two molecular classes according to their gene expression profile, with metastatic disease occurring almost exclusively with class 2 tumors, which have a high mortality (Onken et al., 2004). A 15-gene assay has been developed, which shows high sensitivity and specificity, even with very small samples and formalin-fixed specimens (Onken et al., 2010).

2.4. Other predictors

Increased mortality is associated with many other factors, whose discussion is beyond the scope of this article. These include: insulin-like growth factor-1 receptor; inducible nitric oxide synthase; increased ezrin expression; and low Heat-Shock-Protein-27 (HSP-27) expression (Ericsson et al., 2001; All-Ericsson et al., 2002; Johansson et al., 2009; Makitie et al., 2001a; Jmor et al., 2010). Interestingly, G protein alpha subunit q (GNAQ), which occurs in about 50% of uveal melanomas, does not correlate with survival (Bauer et al., 2009).

3. Statistical methods

3.1. Kaplan–Meier analysis

Kaplan–Meier analysis is the standard method of reporting cancer survival and plots the proportions of patients surviving at different time intervals. Each death is represented by a step in the curve with the size of the step depending on the number of survivors at the start of the interim period. When the curves represent metastatic mortality, non-metastatic deaths are treated like other causes of incomplete follow-up and are censored, with censoring indicated by ticks in the curve. Because of censoring of non-melanoma deaths, it is not possible to deduce from Kaplan–Meier curves a patient’s chances of dying from melanoma or the chances of surviving a specified time. This is because such censoring exaggerates the apparent metastatic mortality to give a false impression of the survival probability (Kujala et al., 2003). For example, older patients appear to have an increased risk of metastatic death (Fig. 4). When statistical methods take account of competing risks, however, older people are actually found to be less likely to die of metastasis because more of them have died of other causes before the metastatic disease has had time to develop (Fig. 4). Similar difficulties

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Fig. 2. Kaplan–Meier survival curves showing metastatic mortality to correlate strongly with: (A) Ciliary body involvement (logrank, $p = 0.001$); (B) Basal tumor diameter (logrank, $p < 0.001$); (C) Extravascular spread (logrank, $p = 0.002$); (D) Epithelioid cytomorphology (logrank, $p < 0.001$); (E) Closed loops (logrank, $p < 0.001$); (F) Mitotic rate (logrank, $p < 0.001$); (G) Chromosome 8 gain (logrank, $p < 0.001$); and (H) Chromosome 3 loss (logrank, $p < 0.001$). Metastatic death occurred in 12 patients without apparent chromosome 3 loss, encouraging the authors to use MLPA instead of FISH. With permission from Damato et al. (2007).

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occur when comparing males with females, because competing risks are greater in males. Kaplan–Meier analysis has other limitations, such as not allowing multivariate analysis and not coping with continuous variables such as basal tumor diameter. For these reasons, if used for purposes other than comparing randomized groups of patients, Kaplan–Meier survival curves are all-too easily mis-interpreted by those who are not aware of all the causes of bias. They do not allow accurate prognostication. A variety of methods
have been developed to take competing risks into account, as in the study by Kujala et al., cited earlier.

A problem with mortality statistics is that they depend greatly on the accuracy with which the cause of death is diagnosed. With uveal melanomas, this shortcoming is significant because many patients die at home, far from the oncology center that treated them. Hepatic metastases from colon cancer can mistakenly be attributed to uveal melanoma, for example, whereas fatal cardiac arrhythmia from metastases may be mis-diagnosed as ischemic in origin (Makitie and Kivelä, 2001). Fortunately, because uveal melanomas are so rare, it is possible to estimate the metastatic mortality without depending on the certified cause of death (Hakulinen and Dyba, 2007). This is done by comparing the all-cause mortality of the patient population with that of the general population matched for age and sex. We are fortunate in obtaining reliable mortality data from the National Health Service (NHS) Cancer Registry on all patients resident in mainland Britain, who are flagged by their NHS number.

3.2. Liverpool Uveal Melanoma Prognosticator Online (LUMPO)

We have developed an online tool that generates an all-cause mortality curve according to age, sex, TNM size category (based on basal tumor diameter and tumor height), ciliary body involvement, melanoma cytomorphology, closed loops, mitotic count, chromosome 3 loss, and presence of extraocular spread (www.ucularmelanomaonline.com). It also categorizes tumors according to their TNM stage.

Previously, we relied on neural networks, which were trained using data from patients treated by local resection or enucleation (Damato et al., 2008). However, these were found not to cope well with imputation procedures dealing with missing data, such as closed loops and mitotic count, which could not be assessed in tiny
to more than 20 years. The performance of the model was assessed by bootstrap re-sampling (i.e., randomly splitting the entire dataset into training and test datasets 200 times) (Eleuteri et al., in press). LUMPO produces estimates that are accurate enough to be relevant to individual patients (Fig. 5) (Eleuteri et al., in press). This is because the multivariate analysis includes not only clinical features but also histologic grade of malignancy and genetic tumor type. Fig. 6 shows the importance of including all these factors in the prognostic model.

The program also generates a survival curve for the general British population matched for age and sex (Fig. 6). This enables the metastatic mortality to be estimated, as mentioned before (3.2). The 95% confidence intervals are plotted to indicate the reliability of each prediction. A pictogram is also drawn, to facilitate communication with patients.

Such ‘personalised prognostication’ has significantly changed our clinical practice. Further studies will be needed to determine whether LUMPO can be used with non-Caucasians and with patients in other centers and countries, whose life-expectancy may be quite different to that of British patients treated at our hospital.

4. Harvesting tumor tissue for prognostication

Between 1999 and 2007, we performed genetic typing and histologic grading only on tumors treated by enucleation or local resection; prognostication on irradiated tumors was based only on tumor dimensions and extent. In 2007, we started performing prognostic biopsy on such cases. This was because our experience had convinced us of the clinical benefit of accurate prognostication and the need for multivariate analysis using histologic and genetic data.

For patients treated with brachytherapy, we perform fine-needle aspiration biopsy using a 25-G beveled needle, which is passed obliquely through the sclera overlying the tumor immediately before inserting the radioactive plaque. In patients having a post-equatorial tumor and those treated with proton beam radiotherapy, we perform the biopsy within days of completing the radiotherapy, using the sutureless, trans-conjunctival, 25-G vitrectomy system. We are still auditing these procedures, to assess the adequacy of the tumor samples and determine the incidence and outcome of complications such as episcleral tumor seeding, vitreous hemorrhage, rhegmatogenous retinal detachment, and endophthalmitis. Interim results suggest that our success rates have not been as high as those reported by some other authors (Shields et al., 2011). Biopsy forceps have been developed to enhance the yield (Akgul et al., 2011).

5. Scope of prognostication

5.1. Clinical care

We have found that almost all of our patients want to know their prognosis for survival, whether this is good or bad and even when they are told that prognostication is most unlikely to improve their chances of prolonging life (Cook et al., 2008). In-depth psychological studies have shown that patients given a poor outlook only rarely regret their decision to have prognostication (Cook et al., 2008). Although bad news is indeed upsetting, patients develop compensatory mechanisms and feel a sense of empowerment over their future planning, which they value (Cook et al., 2010). Interestingly, patients find a poor prognosis less upsetting than an uncertain prognosis (Cook et al., 2010). The patients who are most distressed are those who cannot be given an accurate prognosis because genetic testing has failed. Some might question whether patients are able to provide informed consent for prognostication, especially when they also need to decide on their ocular treatment.
at a very stressful time. However, this is not a significant problem, as our own studies have shown (Cook et al., 2010).

Patients receiving a good prognosis tend to be reassured by the news, but some remain sceptical so that special measures need to be taken to convince them of their good fortune (e.g., informing them of evidence base). One patient became extremely upset on being informed that his diffuse melanoma was of spindle-cell, disomy-3 type and therefore likely to be non-lethal: he wrongly concluded that his eye had been enucleated unnecessarily. He had been sent the good news by mail but had ignored our advice to discuss this letter with our specialist nurse by phone, instead making a formal complaint directly to the chief executive of our hospital. We were, however, able to reassure him of the necessity of the operation, despite the tumor’s relatively low-grade malignancy. This mishap taught us that the response to prognostication can be unpredictable so that it is important to proactively encourage questions and discussion, if possible in person.

Patients’ attitudes to prognostication, as well as their reaction to their survival predictions, are likely to vary according to their age, gender, social class and nationality, not to mention the way in which they are counseled by their medical practitioner. Further studies are therefore needed to determine whether our experience is replicated in other centers and countries.

Thanks to our prognostication methods, we have been able to screen high-risk patients for metastatic disease and have identified resectable hepatic metastases in a small number of patients, some of whom have enjoyed prolonged survival (Fig. 7).

Screening for metastases from uveal melanoma is expensive and causes significant stress to patients, especially if they have to travel long distances or if there is a false-positive result, which is not uncommon. Further studies are needed to determine whether prognostication and screening actually prolong survival.

5.2. Research

There is scope for randomised trials evaluating different forms of systemic adjuvant therapy, in the hope that metastatic disease and death might be delayed or even prevented altogether, as has been achieved with orbital rhabdomyosarcoma, breast cancer and other malignancies. Unfortunately, previous studies with uveal melanoma have failed to show statistically-significant benefit (Desjardins et al., 1998). A recent study investigating intrahepatic fotemustine showed a non-significant trend toward improved survival (Voelter et al., 2008). However, the high-risk patients were selected only on the basis of large tumor size, and from our own data we estimate that about 25% of these are likely to have had a non-lethal melanoma. Presuming that the observed difference was real and not due to chance, if prognostication had also been based on histologic and genetic data, albeit with slower accrual, then patients with non-lethal melanoma would not have been

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enrolled in this study and a statistically-significant result might have been obtained, changing clinical practice. There is also a need for randomised trials evaluating the impact of ocular treatment on metastatic disease. It is not known whether ocular treatment of uveal melanoma ever influences survival and if so in whom (Damato, 2010). Enucleation has at various times been considered to prolong life, shorten life, and to be inconsequential. Similarly, it is not known whether the risk of metastatic death is iatrogenically increased by surgical manipulation, local tumor recurrence and treatment delays. Randomised trials have either been impossible or under-powered (e.g., Collaborative Ocular Melanoma Study (COMS)) (Damato, 2007). This is because approximately 1000 patients would need to be studied (Tishkovskaya, S et al., unpublished data). Because many patients are likely to be lost to accrual or follow-up, at least twice this number would need to be enrolled and this would require international, multi-center studies, which would be difficult and expensive to organize.

6. Putting theory into practice

When counseling new patients with uveal melanoma, we offer prognostication, discussing the risks and benefits, taking account of each individual’s general health and personality. We provide them with an audio-recording of the consultation on CD-ROM or cassette to help them remember what they were told. Consent is requested for the use of their samples and data for research. Fresh tumor samples are obtained from excision or biopsy specimens for histologic and genetic studies. These investigations are now performed in our hospital, by experienced staff working in an accredited pathology laboratory, and, in addition to free text, synoptic reports are issued to avoid ambiguity. Quality control laboratory studies are performed in collaboration with other centers. Data are prospectively computerised into our ocular oncology database/patient management system by a full-time data manager and these data are used routinely for clinical care, audit and research. The clinical, histologic and genetic data are entered into an online form (i.e., LUMPO) (3.2) to obtain a personalised survival curve. A printout of this survival curve is sent to the patient’s referring ophthalmologist, family doctor and to our medical oncologist, together with a covering letter, explaining the significance of all results and the proposed management plan. The charts are reviewed so that this letter takes into account of the patient’s age and general health. In our covering letter and in any counseling, we note the width of the confidence intervals relating to the survival curves and explain that...

Fig. 7. A 48-year-old man was referred in 2007 with an amelanotic choroidal melanoma in the right eye (A). The tumor measured 8.7 mm x 7.9 mm in basal diameter with a thickness of 2.2 mm (B). The patient had a biopsy and a trial of photodynamic therapy was commenced, the patient accepting that this was not standard treatment. Because of the small tumor size we would not normally have recommended life-long screening for metastasis, estimating the 10-year metastatic mortality to be approximately 10%. Histology revealed epithelioid cells and MLPA showed chromosome 3 loss and gains in chromosome 8q (C). The photodynamic therapy was abandoned and the patient was treated with proton beam radiotherapy, which is more reliable. Multivariate analysis indicated a 19% risk of metastatic death in 8 years and the patient underwent 6-monthly MRI. In 2009, two lesions were detected in the right lobe of the liver and these were resected without complication. A year later, metastases developed in the left lobe of the liver as well as in bone and lungs. The patient was treated with ipilimumab and was still alive in mid-2011, when this article was written. The patient may not have survived as long if biopsy had not been performed and if his metastases had not been detected at a later stage.

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estimates of life-expectancy may turn out to be wrong or misleading. For example, of the patients who are reassured by a 90% chance of surviving ten years, there will be 10% who develop metastatic disease sooner than this. Even though all patients are informed from the outset that prognostication involves approximation, there is scope for formal psychological studies assessing how such patients react when metastatic disease develops unexpectedly. It has been suggested that molecular testing of uveal melanomas must demonstrate high reproducibility, reliability and validity before it is introduced into clinical care (Harbour, 2009). Although such an ideal is desirable, if clinical deployment of genetic testing were to be delayed until high levels of reliability are proven, then it would be necessary to rely on crude indicators such as tumor size and patients would be deprived of meaningful prognostication. We believe that a more realistic approach is to offer the best methods available, following the principles of good laboratory and medical practice whilst addressing technical limitations and clinical uncertainties appropriately.

If the patient has an excellent survival probability, a letter is sent to the patient giving the good news, explaining that there is little scope for systemic screening. This letter is followed by a telephone call from a specialist oncology nurse to discuss the result. An individualised screening policy is formulated on a case-by-case basis, taking the patient’s wishes and fears into account.

If the patient has a high risk of metastatic disease, an appointment is made at our clinic to discuss the result and its implications, to undergo liver imaging and liver function tests, to receive counseling from our health psychologist, and to make arrangements for further management. Depending on the level of risk and the patient’s ability to commute, further care is continued at our clinic or at our oncologist’s hospital or at the patient’s local hospital, in which case a detailed information pack is sent to the local hospital. Patients developing metastatic disease are entered into various trials, being led by the Liverpool Clinical Trials Unit and supported by the National Cancer Research Institute Melanoma Group. It is hoped that before long it will be possible to enroll high-risk patients into trials of systemic adjuvant therapy.

Quality of life and other patient-related outcomes (e.g., difficulty reading) are measured by sending patients a questionnaire after six months and then on every anniversary of their treatment.

7. Future directions

It is likely that over the next few years there will be further advances in biopsy techniques as well as histologic and genetic methods. There is scope for greater standardisation with regards to measuring tumor dimensions, performing laboratory investigations, categorising melanoma cytomorphology, defining genetic tumor type and diagnosing cause of death.

We anticipate that we will continue training and evaluating our prognostic model (i.e., LUMPO) and that as the dataset expands we should be able to incorporate more predictors (e.g., chromosome 6p gain). There is scope for investigating whether the multivariate model would be enhanced by host factors, such as lymphocytic and macrophage infiltration and macrophage density, which we have not so far recorded. With patients having rare combinations of predictors we expect that in time greater numbers should make it possible to improve the precision of survival estimates, so that confidence intervals become narrower. We also hope to lengthen the survival curves well beyond ten years as follow-up times increase. At present, we use general population data to estimate the likelihood of metastatic death, but we hope to be able to make personalised adjustments if an individual patient’s life-expectancy is known to be diminished by known lifestyle factors or disease. Progress in prognostication would be accelerated by multicenter collaboration, which should become more feasible as biopsy, histologic grading and genetic typing become more widespread. There is scope for multicenter studies to determine whether methods used in one unit are reliable elsewhere and to compare rival techniques and strategies. We are in the process of developing an online tool to enable workers from other centers to determine whether LUMPO is relevant to their data.

If prolongation of life is achieved in more patients as a result of hepatic or systemic treatment, then statistical methods will need to be developed to deal with any bias caused by such therapy.

Until now, we have relied solely on qualitative methods to measure psychological responses to prognostication. There is scope for quantitative studies statistically correlating quality of life with the survival prognosis and for several years we have been collecting data prospectively for this purpose.

The TNM staging manual does not yet advise on merging clinical and laboratory tumor data. There are only recommendations for collecting data and suggestions for histologic grading. However, moves are afoot to improve the TNM system so that it uses all available data.

In conclusion, the accuracy of prognostication is greatly enhanced by multivariate analysis of clinical, histologic and genetic data, also taking age and sex into account. Kaplan-Meier analysis is inadequate because it does not cope with continuous variables and competing risks. Cox proportional hazards model is not possible because the hazards are not proportional. We have developed and validated online prognostication tools that are accurate enough to be relevant to individual patients.

Patients with a “low-risk” uveal melanoma are more likely to enjoy a good quality of life if they can confidently and reliably be informed of their excellent prognosis, especially if they are spared unnecessary screening for metastatic disease. Special precautions are needed to avoid misunderstandings from arising.

Patients with a high risk of metastatic disease tend to develop coping mechanisms so that their quality of life is far better than one might expect. At least in Britain, they do not regret being informed of their prognosis because they want to be empowered to sort out their personal affairs and do all they can to improve their chances of survival.

Improved identification of “high-risk” patients has led to targeted screening for metastatic disease and better opportunities for clinical trials evaluating different treatments for metastatic disease. More accurate prognostication also enhances prospects for randomised trials evaluating systemic adjuvant therapy as well as basic science research.

These benefits have come about because of simple yet robust protocols and infrastructures that have enabled us to prospectively collect and computerise clinical and laboratory data and outcomes uninterruptedly for over one-quarter of a century.

The prognostic methods we have developed for ocular oncology should be widely applicable, not only in ophthalmology and oncology but also in other fields of medicine.

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