CAN PERIODIC SURVEILLANCE FOR METASTASES IMPROVE CLINICAL OUTCOME IN UVEAL MELANOMA? MOVING TOWARDS INTERNATIONAL GUIDELINES

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ABSTRACT

Uveal melanoma is a rare disease with a predominant propensity for liver metastasis. Prognosis in the metastatic setting is poor, and no treatments have been proven to extend survival to date. Surveillance for metastases is commonly performed in practice, although there is no unequivocal evidence of its benefit. Surveillance is however intuitively advantageous, allowing locoregional management of liver-only metastases, and facilitating early systemic treatment and particularly trial enrolment, and should, in our view, be considered good clinical practice. Several questions remain, including whom to screen, what modality to use, and for how long. In addition, further investigation is required into the incorporation of novel biomarkers and adjuvant strategies into surveillance.

Keywords: Uveal, melanoma, metastatic, screening, high risk.

INTRODUCTION

Uveal melanoma (UM), is the most common primary malignancy of the eye, but remains a rare disease, with an incidence level of around 5-10 cases per million of the population being reported in Caucasians.[1-3] Despite a high rate of local control with treatment, between 30% and 50% of patients will subsequently develop metastases.[3-5] Prognosis in the metastatic setting remains poor, with a median survival of less than 6 months.[4,6,7] Notably, the clinical course of UM is distinctive from cutaneous melanoma (CM), with metastases predominantly (and often exclusively) occurring in the liver. Surgical management of liver metastases offers the only real likelihood of long-term disease control at present,[8,9] particularly as there are currently no proven systemic therapies for UM (reviewed in[10,11]).

The well-recognised natural history of UM has led to the hypothesis that surveillance may enable early identification of liver metastases, in turn facilitating locoregional management and improving survival within the disease. Internationally, many centres now perform periodic screening of patients with UM. However, the optimal screening modality (e.g. computed tomography scanning (CT), magnetic resonance imaging (MRI), and ultrasound scanning (USS)), timing, duration, patient selection, and overall benefits of surveillance remain highly contentious.

SURVEILLANCE AND SURVIVAL

The most important question relating to any screening is whether this leads to an improvement in survival in the screened population. This has proved extremely challenging in surveillance of metastatic cancer, even for example, in the setting of ovarian cancer, a malignancy with a sensitive biomarker and active therapeutics.[12] Perhaps not surprisingly, a survival advantage has not been demonstrated in UM to date, and a recent review of studies that investigated periodic surveillance from 1980 to 2009 by Augsberger et al.[13] failed to find evidence of a survival benefit associated with regular surveillance. However, the majority of studies were small, retrospective, and from single institutions. In addition, a wide range of screening methods and strategies were described, further complicating the comparison. Notably, none of the studies were

a prospective comparison of surveillance versus no surveillance. Moreover, since these studies were published, significant advances have been made in terms of the sensitivity and specificity of imaging technology, and additional systemic and locoregional treatment approaches have become available.

Demonstrating a survival benefit with regular screening in future trials is likely to prove challenging in a rare disease such as UM. This is compounded by the widespread uptake of surveillance by patients and clinicians, thus making it unlikely that future studies, comparing surveillance with no surveillance, will find favour in the medical community.

However, in the absence of direct evidence linking surveillance to improved survival, the benefit of surveillance may be assessed indirectly by looking at a number of linked questions: does surveillance detect metastases before symptoms develop? Does early detection increase the proportion of patients who can receive treatment or access clinical trials? Does such treatment improve survival, and is this what patients want?

Asymptomatic Detection of Metastatic Disease

The first of these questions is relatively straightforward; with several studies having clearly demonstrated that periodic liver imaging allows the identification of liver metastases prior to the development of symptoms.[14-17] In the study by Marshall et al.[16] for example, 92% of patients who developed metastases, were asymptomatic at the time of diagnosis using 6-monthly non-contrast MRI surveillance. Furthermore, liver surveillance allowed detection of liver metastases in the majority of patients prior to changes in serum biochemistry.

Access to Treatment

Does surveillance increase the proportion of patients who receive treatment? There is limited trial data to support this, although intuitively, patients with low metastatic tumour burden are clearly more likely to access treatment and benefit. It is noteworthy that non-screened patients with metastatic UM typically present, with high tumour burden, deranged liver function and poor performance status. In a retrospective analysis of patients identified by screening utilising liver function tests (n=90) or symptomatically (n=259), there was no statistical difference of patients receiving some form of treatment (66.7% versus 59.5%).[17] However, those patients detected by symptoms had a median survival of only 2.7 months, indicating a high burden of disease and very limited time in which to intervene therapeutically. In contrast, in the study by Marshall et al.,[16] median overall survival (OS) was 12 months in patients with metastases. While the improved survival is clearly at least partly due to lead time bias, this does potentially allow for more therapeutic options, which included surgery in 14% of relapsed patients.

Does Treatment Improve Survival?

To date, there is no unequivocal evidence demonstrating a survival advantage for any treatment modality. This is, at least in part, due to a poor historical evidence base consisting largely of single centre retrospective series or single arm cohort studies. However, two main approaches to treatment have evolved: locoregional therapies – including surgical resection – and systemic therapy.

LOCOREGIONAL THERAPIES

Resection of Liver Metastases

Although no randomised data are available, several retrospective studies hint at prolonged disease control following R0 resection of liver metastases. In the largest case series of 255 patients who underwent surgery for UM metastatis to the liver, Mariani et al.[8] reported a median survival of 14 months, which increased to 27 months in patients who underwent R0 resection. Similar results were observed in a retrospective study of 558 patients with UM, 74 of whom developed metastases. The median overall survival from detection of metastasis was 3.7-fold higher in patients who underwent hepatectomy, compared with those who did not undergo surgery.[18] In the prospective study by Marshall et al.[16] the median survival was 24 months in patients who had surgery, and only 10 months in patients with inoperable metastases.[16] None of these series represent randomised controlled trials, but they do support the concept that resection may have a role to play in a small subset of patients. It remains to be shown whether the number of patients eligible for resection might be increased with greater screening intensity and sensitivity.

Non-Surgical Locoregional Treatment of Liver Metastases

Liver metastasectomy is only possible in approximately 10% of cases using historical screening programmes,[5,16] and consequently, there has been a significant drive to develop

alternative treatment modalities for liver-only metastases. These include radiofrequency ablation, transarterial chemoembolisation (TACE), the use of radiospheres, drug-eluting beads or percutaneous hepatic perfusion (PHP) of chemotherapy. The vast majority of series investigating the efficacy of these treatment modalities were not designed, or powered to determine a survival benefit (reviewed by Sato et al.[5] in 2010). However, many highlight the correlation between lower tumour burden (maximum tumour diameter, percentage liver involvement) and improved outcomes. Only two randomised controlled trials have been completed and these are yet to be published in peer reviewed journals. Both suggest a higher response rate (RR) and progression free survival (PFS) with regional therapy. In a trial comparing PHP with melphalan to investigator-determined therapy, RR of 34.1% and 2% were observed in the experimental and control arms respectively overall, while hepatic-PFS was similarly better in the experimental arm (245 versus 49 days).[19] While overall survival had not improved, the analysis was hampered due to a proportion of patients in the control arm crossing over to PHP melphalan on progression.[19] The second study compared hepatic intra-arterial administration (HIA) and intravenous administration of fotemustine, and showed improved RR (10.5% versus 2.4%) and median PFS (4.5 versus 3.7 months) with regional therapy, although again overall survival was not significantly altered.[20]

Systemic Therapies and Trial Entry

Surveillance leads to the identification of a cohort of asymptomatic patients who are fit enough to receive systemic therapy, in contrast to patients present who are symptomatic and whose organ function frequently precludes treatment. Historically, there has been little evidence to support benefits of systemic therapy, at least in a group of patients with high tumour burden.[10,11] More recently, there is some reason for enthusiasm, with significant progress in immunotherapy and novel targeted therapies in cutaneous melanoma.[21,22] Notably, constitutively active mitogen-activated protein kinase (MAPK) signalling secondary to GNAQ/GNA11-activating mutations is frequently observed in UM, and presents a potential therapeutic opportunity. Preliminary results from a trial of the MEK inhibitor, selumetinib, support this exciting concept, with an increase in both PFS and OS compared to temozolomide.[23]

Moreover, identification of asymptomatic patients facilitates trial entry, and with a plethora of novel agents in development, will in turn enable collaborative large randomised phase II and phase III trials for the first time in this rare disease. Notably, in the surveillance trial by Marshall et al., the study led directly to the initiation of the first UK national portfolio of clinical trials.[24,25] Ultimately, 23 out of the 90 patients with metastases went on to receive treatment in either a national or international trial. The International Rare Cancer Initiative (IRCI) was established in 2011 with the objective of promoting international clinical trials in rare cancers, including UM. The IRCI brings together the National Cancer Institute (NCI) in the US, the UK National Institute Health Research (NIHR), Cancer Research Network (CRN), Cancer Research UK (CRUK) and the European Organisation for Research and Treatment of Cancer (EORTC); and now offers the platform to perform such studies in a truly collaborative approach, and with the prospect of delivering rare cancer trials in a timely fashion.

Patient Wishes

In the absence of clear evidence, clinicians must also work with patient partners to determine optimal care and follow-up. Furthermore, refined prognostication[26,27] is creating an increasing cohort of well-informed patients requesting detailed assessment of relapse risk and survival. We have found that almost all of our patients want to know their prognosis for survival, whether this is good or bad, even when they are told that prognostication is most unlikely to improve their chances of prolonging life.[28] In-depth psychological studies have shown that patients given a poor outlook only rarely regret their decision to have prognostication.[28] Although bad news is indeed upsetting, patients develop compensatory mechanisms and feel a sense of empowerment over their future planning, which they value.[29] Against this background, patient groups are increasingly advising UM patients to seek out surveillance in specialist centres as one aspect of planned care and follow-up (e.g. OcuMel (UK), CUREOM (USA)) as an aid to access early treatment.

SURVEILLANCE: WHO, HOW, HOW OFTEN AND HOW LONG?

Selection of Patients for Surveillance

The risk of metastatic relapse in UM is determined by multiple factors, including clinicopathological features such as tumour thickness[30] and cytogenetic abnormalities, most notably the loss of chromosome 3.[31] In addition, the risk of recurrence may be assessed using multigene expression assays.[26] This has enabled

the development of sophisticated prognostic tools, which allow the identification of patients with a high risk of developing metastases,[26,27] for whom surveillance is most likely to be beneficial. Targeted screening, in the highest risk patients with the greatest needs, also offers a practical setting where clinical trials may be most helpful in elucidating the role of follow-up. In the study by Marshall et al.[16] for example, only patients with monosomy 3 were enrolled, thus limiting surveillance to patients with a high risk of recurrence, which is reflected in the development of metastases in 48% of patients, after a median follow-up period of approximately 29 months. Conversely, patients for whom relapse is very unlikely may be reassured and discharged early. However, the level of risk that is employed as a cut-off is clearly subject to debate. The risk/benefit ratio of screening in low risk disease poses additional challenges and must be carefully weighed against potential harm from false positive findings, potential radiation exposure, psychological morbidity and the economic impact.

Optimal Surveillance Modality

Many different imaging modalities are in use or have been suggested; including, but not limited to, liver imaging with USS, CT or MRI (with or without contrast enhancement) or body imaging with CT or Positron Emission Tomography-CT (PET-CT). The choice of imaging modality currently reflects local practice access and whether or not to exclusively image the liver or include extrahepatic sites.

The principal hypothesis behind screening is the detection of resectable liver metastases, which has in turn led to the use of liver imaging as the primary modality used for screening. This is in turn predicated on the assumption that a significant proportion of patients have liver-only metastases, which is in the main borne out by the evidence. In an imaging study of 110 patients, 55% had liver-only metastases, and the liver was involved in 92% overall.[32] Several other studies have similarly reported high rates of liver involvement.[33-36] In a series evaluating distribution of metastases at death, the liver was involved in 93%, although in 87% of cases there were multiple sites of metastases.[37] Even at this late stage however, a second autopsy series showed liver-only metastases in 30% of patients.[38]

Many of the published studies represent case series with variable stage of presentation and hence the frequency of extrahepatic metastases at first relapse remains unclear. Recent case series utilising PET-CT have illustrated that UM metastases can be widely disseminated and include unusual sites such as cardiac, muscle, and thyroid etc.[39,40] Extrahepatic relapse in the absence of liver metastases appears uncommon although, prolonged survival has also been described following solitary extrahepatic metastatectomy.[41] The low frequency of isolated extrahepatic relapse would not appear to justify routine imaging beyond the liver, especially given the potential harmful radiation effects of long-term CT follow-up.[42]

Liver Imaging

Although there has been very limited formal evaluation of imaging in UM, a meta-analysis in gastrointestinal cancer reported the highest weighted sensitivity in the detection and assessment of liver metastases with either MRI or PET-CT.[43] Two uveal-specific studies suggest that MRI may be superior to PET-CT in detecting small hepatic metastases (lesions <10 mm in diameter).[44,45] Although, MRI still remains an imperfect preoperative modality, given the pattern of military liver metastases that is frequently noted in UM. Contrast-enhanced MRI can further increase high spatial resolution and sensitivity and is the preferred liver-imaging technique for potentially operable malignant liver disease. The role in routine surveillance is less clear and potentially offset by high costs, long procedure time and a recognised low incidence of potentially adverse reactions. A direct comparison between MRI with and without contrast has not been published in UM. Investigation into the utility of PET-MRI in this setting is also required. This is a relatively new technology, which is not in general use at present. However, PET-MRI has potential advantages, most notably the absence of ionising radiation, and it has been shown to be better at detecting small colorectal liver metastases compared to PET-CT.[46]

The choice of modality clearly has implications on the cost-effectiveness of any surveillance programme. The estimated costs to our institution are £85-125, £380, £370, £450 and £900 for liver USS, contrast CT, non-contrast MRI, contrast MRI and PET-CT respectively. In the absence of cost-effectiveness data, the choice of modality has been based upon a relatively subjective assessment of efficacy in relation to cost and the scope of the surveillance programme (all patients versus a targeted high risk population).

Serum Biomarkers

Circulating biomarkers may offer a potential screening tool in the future, but remain largely experimental at present. Traditional serum markers, such as liver function tests and lactic dehydrogenase (LDH), have very low sensitivity and identify patients who are symptomatic and/or are less likely to respond to treatment as previously described. However, more recent work into circulating tumour cells[47] and serum-free DNA[48] suggests that these techniques may be worth investigating as biomarkers for the early identification of metastases.

Frequency and Duration of Follow-Up

There is very little evidence on which to base decisions regarding either frequency or duration of follow-up. In a study by Eskelin et al.[14] surveillance was performed annually using liver USS and 59% of metastases were detected at an asymptomatic stage. The authors hypothesised that 6-monthly imaging would increase the percentage of asymptomatic detection to 95%, and indeed, in the study by Marshall et al.[16] (in which surveillance was performed every 6 months), 92% of patients were detected before the development of symptoms. The latter study, however, used a different and potentially more sensitive screening modality, namely liver MRI, which clearly complicates comparison of these two trials. Nonetheless, the general consensus in the field is that 6-monthly imaging is preferable.

UM may continue to relapse for many decades following primary diagnosis, with 20-33% of deaths attributed to metastatic recurrence even at 15-35 years.[49] The role of lifelong screening is unknown, but it is pertinent to note that surgical resection series report that the outcome appears most favourable in later relapsing patients, perhaps arguing for prolonged follow-up in some instances. Lifelong screening in all patients would appear unjustified and expensive, and supports the concept of targeted screening of higher risk subgroups. Marshall et al.[16] reported that 65% of high-risk patients had relapsed at 5 years on non-contrast liver MRI surveillance, and thus focusing surveillance on this period would appear sensible. However, a further period of screening, albeit at a lower intensity, may also prove to be of value in the detection of resectable disease.

CONCLUSIONS

Based upon experience in more common cancers, it appears highly unlikely that definitive screening trials will ever be completed in the rare setting of UM. Furthermore, survival may be an unrealistic endpoint of such research. Surveillance is intuitively advantageous, allowing locoregional management of liver-only metastases, and facilitating early systemic treatment and particularly trial enrolment before the disease burden causes deteriorations in general health and performance status. Additionally, surveillance facilitates patient follow-up, provides a link with oncology services and allows a more holistic approach to cancer patients that includes early access to cancer nurse specialists and smooth transition to services such as palliative care at an appropriate stage. These factors strongly suggest that the use of periodic surveillance is a good clinical practice, although questions clearly remain.

In our opinion, sophisticated prognostication linked with targeted liver screening of high-risk patients should be the preferred option. This should be carried out within a specialist multidisciplinary team that incorporates expertise from ophthalmology, oncology, cancer nursing and hepatic services. While the optimal surveillance programme remains debatable, our current practice is to target high-risk patients and perform 6-monthly surveillance incorporating a clinical review, nurse specialist support, blood for putative circulating biomarkers and non-contrast liver MRI for the first 5 years. Beyond 5 years, patients are counselled with the option to continue lifelong surveillance with annual follow-up thereafter.

However, if real progress is to be made, well-designed collaborative multicentre international trials, that incorporate novel biomarkers and modern imaging modalities, are essential. These trials should run alongside, or incorporate, investigations into potential adjuvant strategies. Such trials will in turn provide vital evidence to underpin much needed international guidelines in this rare disease.

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