Predictive power of screening tests for metastasis in uveal melanoma

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Abstract

Purpose Uveal melanoma undergoes haematogenous dissemination, particularly to the liver. It is routine practice to screen for metastatic disease. The purpose of this study was to evaluate such screening tests and to determine their value in detecting metastatic disease at presentation.

Methods In this study of a series of 245 patients with uveal melanoma of whom 55 (22%) died, the sensitivity, specificity, positive and negative predictive powers and likelihood ratio of the blood tests, chest radiographs and liver ultrasound investigations performed at diagnosis were determined.

Results All the screening investigations were found to have a low yield, but the most sensitive were those for gamma-glutamyl transpeptidase (γ GT; sensitivity 21%) and alkaline phosphatase (sensitivity 25%), with γ GT being more specific (specificity 92%). No blood test had a positive predictive power greater than 50%. The chest radiograph and liver ultrasonography were both 100% specific but had sensitivities of 2% and 14% respectively.

Conclusions Only the chest radiograph and liver ultrasonography had positive predictive powers greater than 50% and these tests had very poor sensitivity. We conclude that there is no good test available for screening for metastatic uveal melanoma.

Key words Melanoma, Metastasis, Screening, Uvea

Uveal melanoma is the commonest primary intraocular malignant tumour, with approximately 40% of patients developing evidence of metastatic disease within 10 years of diagnosis.¹⁻³ The commonest site of initial recognition of metastatic disease is the liver,⁴⁻⁸ with the proportion presenting at this site varying in reports from 46%⁴ to 88%.⁸ Ninety-seven per cent⁹ to 100%¹⁰ of patients who die from metastatic melanoma have evidence of liver involvement.

The detection of metastatic spread at diagnosis of uveal melanoma does influence our management of this disease. In particular, we would avoid enucleation, if the eye was not painful, in patients with overt metastatic disease as we would consider that to be needless mutilation. Given the predisposition for spread to the liver, it is not surprising that screening tests for metastatic disease have concentrated on looking for hepatic involvement. The most sensitive blood test described to date is the gamma-glutamyl transpeptidase (γ GT) level.¹¹ Initially the γ GT test looked very promising. About 13% of patients had an abnormal γ GT level at the time of enucleation and they all developed metastatic disease, accounting for half the patients who subsequently developed metastases,¹² and giving a sensitivity of 50%. A subsequent paper from the same group¹³ reported a much lower sensitivity of only 12% (6 of 50 patients) having either abnormal liver function tests or abnormal liver scans at presentation and who subsequently died of metastatic disease.

We routinely perform a full blood count and differential, chest radiograph, test blood levels of the enzymes aspartate-amino transferase, alanine-amino transferase, γ GT and alkaline phosphatase and circulating bilirubin levels, and perform hepatic ultrasonography on those patients due to undergo enucleation. With the exception of the γ GT, the sensitivity and specificity of these tests for screening for metastatic uveal melanoma have not been reported. However, of greater importance to the clinician are the positive and negative predictive powers of the test (i.e. whether or not a positive result is a true positive indicating metastatic disease).

This study was undertaken to determine the sensitivity, specificity, positive and negative predictive powers and the likelihood ratios of the commonly used screening tests.

Methods

The records of a series of patients with ciliary body or choroidal melanoma who had been treated at Moorfields Eye Hospital between 1982 and 1992 were reviewed retrospectively.

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Data were collected from the clinical notes, including age at diagnosis, sex, time to death or length of follow-up if alive, and site of tumour (ciliary body or choroidal). Histological findings, where available, were categorised into spindle cell, mixed or epithelioid cell, and necrotic.

The investigations considered were the chest radiograph and blood investigations: haemoglobin, platelet and white cell counts, and levels of aspartate-amino transferase (AST), alanine-amino transferase (ALT), gamma-glutamyl transpeptidase (γGT), alkaline phosphatase (APH) and bilirubin (BIL). Liver ultrasonography is only performed routinely in our practice on patients due to undergo enucleation. It was also noted whether the patient had been staged by screening tests prior to referral to our unit, in order to obtain an estimate of referral bias.

Results

The records of 245 patients were retrieved, of whom 55 (22.4%) had died. Of the patients who were still alive, the minimum period of follow-up was 24 months, the mean period was 67.8 months and the median 62 months. Of the patients who had died, the shortest time to death after diagnosis was 8 months, the mean time to death after diagnosis 34 months and the median 30 months.

One hundred and thirty-eight (56.3%) of the patients were male, and 107 (43.7%) were female. The site of the tumour was the choroid in 218 (89%) of the patients, of whom 44 (20.2%) had died from metastatic disease, and in the ciliary body in 26 (11%) of the patients, of whom 11 (42.3%) had died. Extraocular extension was recorded in 13 patients, of whom 10 (76.9%) were dead from metastases, whereas of the 232 in whom there was no extraocular extension only 45 (19.4%) had died. Histological findings, where available, also correlated with outcome. Of the 93 (61.2%) patients in whom histology was available, either from biopsy or after enucleation, 48 (51.6%) were found to have spindle cell melanoma of whom 9 (18.8%) had died, 38 (40.9%) had mixed or epithelioid cell tumours of whom 23 (60.5%) were dead, and 7 (7.5%) had necrotic melanoma of whom 4 (57.1%) had died from metastatic disease.

The chest radiograph was not available in 22 patients. This was considered positive if metastases were found and negative if normal, or if any other unrelated pathology was present. The full blood count was not

available in 4 patients; in 2 patients there were specific abnormalities of haemoglobin attributable to other known pathology. For the purpose of this study a microcytic anaemia was considered to be a positive result suggestive of metastatic disease. The platelet count was classed as either normal (–ve) or abnormal in any way (+ve). Any white cell count outside the normal range, suggestive of either bone marrow depression, inflammation or infection, was considered positive in that it might have resulted from metastatic disease.

Liver function tests were available in 235 patients and were classified as either normal (–ve) or abnormally elevated (+ve) according to the laboratory normal ranges.

During the study, liver ultrasound examinations were performed at diagnosis in our centre only when enucleation was planned; thus they were available for only 40 of 245 patients. For the purposes of this study the results were classified as either positive with evidence of metastases, or negative (either normal or showing an incidental abnormality).

One potential explanation for a low yield of positive results on screening is referral bias, that is if the referring doctors screen their patients prior to referral and only refer on patients who are negative on their screen (possibly referring those who have evidence of disseminated disease to their local oncology services). Of the 245 patients, only 14 (5.7%) had been staged prior to referral to our unit, and only 1 had been found to show evidence of metastatic disease. Of the 13 whose staging had been negative for metastases, 3 (23.2%) died during the study period, compared with 51 deaths (22.2%) of those unstaged before referral. This suggests that there is relatively little referral bias.

The findings are summarised in Table 1, giving for each test the sensitivity, specificity, positive predictive power and negative predictive power. The positive predictive power of a test is the parameter of most use to a physician. Unfortunately, positive predictive power depends upon the incidence. Thus the predictive power of the tests depends on the nature of the population screened and the value obtained is therefore specific to that sample. There is no good single statistic that summarises how well a test performs, but the likelihood ratio (LR = sensitivity/1–specificity) probably comes closest, and these results are also summarised in Table 1. If one knows the incidence of disease in the population,

Table 1. Summary of the results of the screening tests routinely employed for detecting metastatic disease

Screening test	Sensitivity (%)	Specificity (%)	Positive predictive power (%)	Negative predictive power (%)	Likelihood ratio
Chest radiograph	1.8	100	100	75	∞
Haemoglobin	0	97	0	77	0
Platelet count	0	98	0	77	0
White cell count	7.3	98	50	78	3.32
Alanine-amino transferase (ACT)	5.7	98	50	78	3.56
Aspartate-amino transferase (AST)	15	89	28	28	1.31
γ-Glutamyl transferase (γGT)	21	92	42	80	2.54
Bilirubin (BIL)	1.9	99	33	78	1.73
Alkaline phosphatase (APH)	25	86	33	80	1.71
Liver ultrasonography	14	100	100	68	∞

one can calculate the post-test odds (PTO). The post-test odds are the pre-test odds multiplied by the LR. The pre-test odds for our sample as a whole are 0.275 (55/190 = the ratio of patients who died divided by the number of patients who survived).

Discussion

Uveal melanoma is well known to have a significant mortality rate, with approximately 40% of patients developing evidence of metastatic disease within 10 years of diagnosis.¹⁻³ Despite this, the proportion of cases with evidence of metastatic disease at presentation is relatively low, the proportions reported in published series being 0.5%,¹⁴ 2.2%,¹⁵ 2.5%¹⁶ and 6.5%.¹⁴ This in itself suggests that there is no good screening test for metastatic disease. Our results support this.

For a test to be useful, the information it provides must be sufficient to alter management. There is still controversy as to whether treating the primary disease actually improves survival. If it is argued that treatment does not affect survival, then screening for metastatic disease is unimportant as treatment is only for local palliation. Alternatively, if it is argued that the aim of treatment is cure (which is our position), then the presence of metastatic disease would make local treatment inappropriate and the patient would need systemic treatment (though the results for treatment of metastatic disease are currently poor¹⁷). It is then a personal decision as to how accurate the test must be to change management. We do not consider a positive predictive power of 50% (equivalent to post-test odds of 1) good enough to deny a patient potentially life-saving treatment.

Although the predilection of metastases for the liver is well established,⁴⁻⁸ screening tests involving measurements of liver enzyme levels all fared badly. None had a sensitivity of greater than 25% and all had a significant false positive rate reducing the positive predictive power, for our sample, to 50% or less.

The white cell count was surprisingly specific for metastatic disease (98%) but had low sensitivity (7%). All the other haematological results proved to be of no value in screening for disseminated disease.

The imaging tests fare better. Both the chest radiograph and liver ultrasonography were 100% specific but the yields are poor, with sensitivities of only 2% for the chest radiograph and an even more disappointing 14% for liver ultrasonography (considering that it was only performed on relatively high-risk cases).

There are several potential ways that these screening tests could be improved. One way in which the blood tests may be improved is to analyse the results not singly but together. If we take it that a combination of both a positive ALT result and either a positive γ GT or a positive APH are required for a patient to be considered positive for screening, then the specificity rises to over 99% for our sample, but the sensitivity falls to only 7%. We also have to be cautious about constructing such

systems for retrospective data, as they often do not perform so well when validated against fresh data, as demonstrated by the original reports for γ GT.^{12,13}

A second way is to develop new blood tests, and recently much hope was placed on the technique of detecting circulating tumour cells by reverse transcription-polymerase chain reaction (RT-PCR), which exploits the unlimited amplification potential of PCR to be able to detect a single cell expressing tyrosinase.^{18,19} Unfortunately while the early reports were hopeful, it, too, has failed to live up to expectation.²⁰

Both the chest radiograph and the liver ultrasonography had excellent specificities but relatively poor sensitivities. These results may be improved by better technology and new techniques. Abdominal MRI has yet to be formally assessed, while the only report for abdominal CT suggests that it offers little improvement over ultrasonography.¹⁵ A limitation of imaging techniques is that while they are relatively good at detecting nodular deposits, they are far poorer at detecting diffuse organ involvement.

Recent experimental work, in an animal model, has provided fresh insight into the 'dormant tumour state' and provides an explanation why it has proved so difficult to detect. In this model, the metastatic deposits are initially not vascularised and do not grow, but the cells are rapidly dividing;²¹ this is due to proliferation being balanced by apoptosis. The onset of overt metastatic disease correlates with the onset of angiogenesis in the deposits. The micrometastases, during the 'dormant state', form cuffs around the blood vessels up to 8 cells deep. In view of their extremely small size it is not surprising that these micrometastases are clinically asymptomatic and are not detectable by either conventional radiology or biochemical disturbances.

The difficulty in detecting micrometastases contrasts with recent improvements in predicting those patients who have them, and are accordingly at high risk of relapse. In particular the presence of monosomy 3²² and the tumour microvessel density²³ seem capable of detecting patients with close to a 100% chance of developing overt metastatic disease. If these reports are verified, then this approach of prediction, rather than detection, of micrometastatic disease may be the more practical, and serious consideration should be given to treating these high-risk patients with adjuvant therapy.

To summarise, the only single tests specific enough to be useful were imaging by chest radiography and liver ultrasonography, and we now carry out these investigations routinely on all melanoma patients before treatment. No single blood test was useful, due to a combination of poor specificities and sensitivities. It was possible to improve the specificity by combining blood results but this was at the expense of reduced sensitivity. We conclude that, for our sample, only a small proportion of metastatic disease was detectable at presentation.

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