
SCREENING FOR UVEAL MELANOMA METASTASIS LITERATURE REVIEW

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ABSTRACT

Local tumour control in uveal melanoma has improved in the last decades. However, 5-year mortality due to metastases from large uveal melanomas remains high. Recently both isolated liver perfusion therapy and chemotherapy have reached encouraging results in improving metastasis survival. As such screening at an early stage, especially for liver metastases, becomes imperative.

MOTS-CLÉS

S100, MIA, melanome uvéal, mélanome métastaté, screening

KEY WORDS

S100, MIA, uveal melanoma, metastatic melanoma, screening

RÉSUMÉ

Le contrôle local du mélanome uvéal a beaucoup amélioré durant les dernières décennies. Néanmoins la mortalité à 5 ans du mélanome uvéal due aux métastases reste très haute. Récemment, les premiers résultats positifs de traitement de ces métastases ont été acquis avec la perfusion hépatique isolée ou par chimiothérapie. Ainsi le dépistage précoce, notamment des métastases hépatiques, devient impératif.

SAMENVATTING

Locale tumorcontrole in het uveamelanoom is de laatste tientallen jaren sterk verbeterd. Niettemin blijft het 5-jaars overlijdingspercentage voor grote oogmelanomen door het toedoen van metastases zeer hoog. Recent werden de eerste positieve resultaten met verbeterde overleving bij metastasering bereikt met geïsoleerde leverperfusie en algemene chemotherapie. Daarom wordt tijdige screening, vooral naar levermetastasen, belangrijker.

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INTRODUCTION

Although local tumour control is no longer a major problem in managing small and medium-sized uveal melanomas, survival has not improved in the last century. Survival at five years is only 57-60% for large tumours (>8-10 mm in apical height and >16 mm in basal diameter) (11, 48). In the last decades, new treatment modalities have been used to improve survival including systemic chemotherapy (58, 61) or immunotherapy. As the liver is frequently involved in uveal melanoma metastasis, and reduces the life expectancy significantly (6), therapy has also been focused on treatment of isolated liver metastasis. Positive effects are reported recently with isolated liver perfusion chemotherapy (6, 43, 59). As such, a screening for early liver metastases becomes more relevant.

It is suggested that on the moment of enucleation, uveal melanomas have already spread haematogenously (21). Nevertheless, only half of these patients also develop macroscopic metastases in later life. It is assumed that at different locations in the body, the tumour stays 'dormant', probably in liver and/or bone marrow (18, 57, 70). The present challenge is to identify and treat metastases early and, if possible, identify and screen a subgroup of high-risk patients. Presently, histologic cell type, largest tumour diameter and tumour location are still regarded as leading prognostic factors in uveal melanoma (56).

Uveal melanoma metastases occur in liver (56-90%), lung (31%), bone (7-23%) and skin (17-36.5%) (5, 10, 44, 67). At time of diagnosis of metastases, 60% of patients have liver metastases and ad mortem 90-100% (44). Few reports are made about cardiac metastases (45, 67), breast metastases (15), brain (52), contralateral choroid (13, 73) and regional lymph nodes (16).

Presently, screening is advised to be (semi-)annual with chest x-ray, liver ultrasound and/or liver function tests, especially in high-risk melanomas (22, 34, 43).

CURRENT GUIDELINES

Up to now, there are no generally accepted guidelines for the follow-up of uveal melanoma patients and screening for metastasis. The Collaborative Ocular Melanoma Study Group (COMS) has proposed an annual physical examination in addition to liver function tests and chest X-ray for their mortality coding study. When metastasis was suspected, confirmation tests, such as CT scans, radionuclide scans, and/or biopsy or cytology were recommended (67, 75). Annual chest x-ray is still contested, also because the relative sensitivity of x-ray for the lung metastasis (detection rate 24%), but is recommended as screening at the time of diagnosis of the primary tumour (12, 67).

CURRENT THERAPIES AND OUTCOME

The current therapies for metastatic uveal melanoma are chemotherapy with or without surgery, chemotherapy in combination with immunotherapy, isolated hepatic treatments and, recently, general immunotherapy (vaccination therapy).

No large randomised trials are published on systemic chemotherapy in metastatic uveal melanoma.

Many uveal melanoma patients are treated with-in current skin melanoma studies (e.g. 42). Intravenous chemotherapy is mostly based on DTIC (Dacarbazine), a standard chemotherapy for cutaneous melanoma. Chemotherapy based on DTIC (Dacarbazine) is of little benefit up to now (2, 5, 6). Nevertheless, patients with only extrahepatic metastasis seem to have a significant benefit of this chemotherapy (24). Recent in vitro studies indicate possible better results for a combination of treosulfan with gemcitabine or cytosine arabinoside (59). Pföhler et al. (61) recently published a pilot study with treosulfan and gemcitabine with an objective response rate of 28.6%. But this still warrants further controlled studies.

The role of surgery in combined treatment is limited to excision of large isolated metastases in the liver, followed by systemic chemotherapy (68).

Chemotherapy in combination with immunotherapy (e.g. interferon, interleukin 2) is also

used. Pyrhönen et al reported (63) that DTIC in combination with bleomycin, vincristine and lomustine (BOLD) and human leukocyte interferon showed a modest result in 3 out of 20 patients. Other studies gave similar results (4, 6, 41). Given the moderate toxicity, BOLD in combination with Interferon might be a reasonable option for patients with extrahepatic metastases. Pyrhönen (63) also showed that a staging based on tumour dimension, Karnofsky index (an assessment scale to measure the patient's overall performance and ability to carry out activities of daily living) and serum alkaline phosphatase levels may indicate a subgroup where chemotherapy may have a better result. Isolated liver metastases are treated with chemoembolisation, intra-arterial hepatic chemotherapy or isolated liver perfusion: a response is reported in 30% (6, 19, 23, 69), 40% (43) and 30-60% of patients, respectively (59). Intrahepatic arterial chemotherapy seems a better option for patients with isolated liver metastasis compared to systemic chemotherapy (6). Immunotherapy based on vaccination with tumour antigens (e.g. Tyrosinase, gp100, MART1, MAGE-genes, HMP, p14, p15, p16, BAGE, RAGE, CDC27, NA17-A, PRAME), is becoming useful in metastatic cutaneous melanoma, but has not been properly tested in uveal melanoma (42, 78).

PATIENT INCLUSION CRITERIA

The COMS study focuses its screening on "large tumours", defined as those for which ophthalmologists agree that the eye should be removed: greater than 10 mm in apical height or at least 16 mm in diameter, and those measuring between 8-10 mm in apical height that were too close to the optic nerve for optimal radiotherapy. All patients had to be metastasis-free prior to enucleation, on the basis of a systemic evaluation that included routine clinical and laboratory examination as well as chest X-ray and liver function tests. The European Organization for Research and Treatment of Cancer (EORTC) defines "high-risk" patients eligible for vaccination as larger than 12 mm in tumour diameter and > 6 mm in tumour height,

older than 18 years and <70 years with normal blood tests (20).

SCREENING METHODS

1. IMAGING TECHNIQUES: LIVER IMAGING

With current imaging technology, one should be able to detect all liver metastases with a diameter of 2 cm or larger, and virtually all of those ≥ 1 cm in size (51, 66). Currently, liver ultrasound is the most frequent choice for detection of uveal melanoma liver metastases and may diagnose liver metastases in 37-78% (6, 43). However, Computer Tomography has been reported to be more sensitive. Leyvraz compared Doppler ultrasound, Computer Tomography, Magnetic Resonance Imaging and Computer Tomography during arterial portography (CTAP) in detection of 30 uveal melanoma metastases (43). Of the 30 metastases detected by intra-operative ultrasound (direct intraoperative assessment of the liver before hepatic intraarterial fotemustine therapy), 29 (97%) had been indicated by CTAP, 23 (77%) by Computer Tomography, 20 (67%) by Magnetic Resonance Imaging, and only 11 (37%) by Doppler ultrasound. In general, ultrasound sensitivity is quoted as 80-90%, and CTAP 85-95%, with dynamic Computer Tomography somewhere in between those figures (28, 30, 72). Positron Emission Tomography-scan has shown to have a sensitivity of 78-93% in metastatic cutaneous melanoma (1). Lately, endoscopic ultrasound in diagnosis of occult liver metastases has also been suggested as it can detect liver metastases in patients in whom non-invasive hepatic imaging studies are normal. However, the frequency at which such lesions are detected is low (62) and its role in screening seems limited at this moment. The cost-effective use of endoscopic ultrasonography, Computer tomography, CTAP, Magnetic Resonance Imaging and Positron Emission Tomography is still to be evaluated in uveal melanoma staging and screening. Scintigraphic imaging of uveal melanoma is at an experimental stage (7, 40).

II. FUNCTIONAL TESTS AND SERUM MARKERS

1. LIVER FUNCTION TESTS

So far, lactate dehydrogenase (LDH) (43), Alkaline Phosphatase (AP) and γ GT (gamma glutamyl transpeptidase) have been found to be relevant in uveal melanoma screening (37). Kaiserman (37) reported early detection of metastases using LDH, ALAT and γ GT in 33 patients. Others have reported a general low sensitivity for liver function tests (22, 35). One of the problems is that liver function tests sometimes seem to rise, but within normal limits. This means that not absolute values, but relative changes should be monitored. Patients with extensive metastatic uveal melanoma with normal liver function tests have also been reported (17).

In general, higher LDH, AP and γ GT are correlated with poor survival. The transaminases and bilirubin seem to be of limited use. Kaiserman showed that in 20% of cases liver function tests could predict metastases earlier than liver ultrasound (37).

2. S100

In cutaneous melanoma S100B has proved to be a valid marker for micro- and/or macrometastasis (33) and of highly prognostic importance (80). It has a sensitivity rate of 80% in advanced metastatic cutaneous melanoma patients (8).

On uveal melanomas, there is a high expression of S100B protein as investigated by immunohistochemistry (9, 79). However, serum S100B was not a prognostic marker in primary uveal melanomas at the moment of enucleation of large tumours (54). Nevertheless, S100B correlates better with metastases than liver function tests or other serum markers (55).

3. MIA

The melanoma inhibitory activity (MIA) protein has been found to be highly prognostic in cutaneous melanoma. Schaller demonstrated that MIA is not of prognostic value in uveal melanoma serum, but is highly upregulated once metastases are present (69). This upregulation was confirmed by others, but MIA could

not predict metastasis earlier than the standard liver function tests (55).

4. CARCINO-EMBRYONAL ANTIGEN (CEA)

In 1976, Shields et al. demonstrated an increase of CEA in metastasized uveal melanoma. As CEA might be increased in many tumours, it has been rarely used in uveal melanoma screening (49-50).

5. 5-S-CYSTEINYLDOPA AND 6-HYDROXY-5-METHOXYINDOLE-2-CARBOXYLIC ACID (MELANIN METABOLITES)

5-S-CD, an intermediate in melanin synthesis, has been found to be of prognostic value in skin melanomas, both in urine and in serum. In uveal melanoma there is only one report on serum, aqueous and vitreous humour of 16 patients (29). 5-S-CD was increased in metastatic patients. 5-S-CD is detected by high performance liquid chromatography (HPLC). HPLC is a rather laborious and certainly not a standard test in clinical chemistry laboratories. S100B, MIA and LDH have proved to predict prognosis better than 5-S-CD in cutaneous melanoma (3, 47). No research has been done yet on 6-H-5-MI-2-C in uveal melanoma. In cutaneous melanoma, 6-H-5-MI-2-C did not prove to be a better prognostic marker than S100B or 5-S-CD (38).

6. TUMOUR SPECIFIC T CELLS

All tumours are characterised by specific tumour-associated antigens and this holds also true for uveal melanoma. Specific melanoma-associated antigens are e.g. MART-1, Tyrosinase (TRP-1), gp100, MAGE1, HMP/NG2, β -catenin, BAGE, RAGE, GAGE, PRAME, ATP6S1, MUM-1, NA17-A (14). These melanoma-associated antigens are presented to T cells by antigen presenting cells, to evoke a tumour-specific cytotoxic reaction. Specific T cells in the blood against these tumour antigens may indicate a generalized tumour spread.

In a non-metastatic patient, however, the tumour load is too low for antigens to be detected up to now [by ELISPOT (enzyme-linked immunospot) or tetramer tests]. Estimations predict that no more than 40 specific T cells would be present among every 1 000 000 peripheral

blood lymphocytes in non-metastatic patients. Therefore these specific T cells are of limited use in evaluating tumour spread (31). An additional problem is that the melanoma antigens are HLA-specific; this means that the same antigens can not be used in the whole population (e.g. 40% of Caucasian population is HLA.A2 positive).

Nevertheless, these techniques have proven to be very useful in monitoring tumour vaccination therapy in metastatic patients, where the number of melanoma-specific T cells is much higher.

7. CIRCULATING TUMOUR CELLS

The detection of tumour cells by PCR screening for upregulated tumour-associated antigens (e.g. tyrosinase) in patient serum, has been tested in many tumours (64). In uveal melanoma, it was possible to detect as few as ten circulating melanocytes in five ml of blood with tyrosinase PCR (77). It seemed of no clinical use as all tested metastatic sera were negative (26); these tests have low reliability and low detection levels. Up to now they failed to predict the likelihood of developing metastatic disease in cutaneous melanoma (32, 65). Nevertheless, Keilholtz et al. found three uveal melanoma patients positive for tyrosinase mRNA in 21 patients, and two of these high risk patients (> 15 mm basal diameter) developed liver metastases within three months (39). Future techniques in detecting circulating tumour cells may improve the current results with immunobead-based detection of cells (25).

III. MICROMETASTASES IN BONE MARROW

As detection of circulating tumour cells is still controversial, bone marrow which is a significant reservoir for micrometastatic cells in general, may be used in detection of micrometastases. In patients with various types of epithelial tumours, the immunocytochemical detection of bone marrow micrometastases has been shown to be of clinical relevance and correlated with melanoma disease-free survival (27, 36, 60, 76). The micrometastatic cells can be detected by immunohistochemistry or RT-PCR on tumour-associated antigens, until now mostly on

tyrosinase. Only one study investigated the bone marrow in uveal melanoma patients and found it to be positive for the 9.2.27 melanoma antibody in 46 (28.7 %) of 161 tested patients, whereas the peripheral blood was only positive in 1 (0.6 %) of the same 161 patients (18).

TUMOUR DOUBLING TIMES IN UVEAL MELANOMA

Several authors reported (21, 46, 72) that based on estimated growth rates, a rational follow-up interval to detect metastatic uveal melanoma would be each 4 to 6 months after diagnosis of the primary melanoma. According to Eskelin (72), systemic micrometastases are present in the body several years before the primary tumour treatment. Besides statistical limitations, these studies do not take in account that the tumour may stay dormant at other places before clinical presentation.

DISCUSSION

The Leiden Screenings Protocol has larger inclusion criteria as the protocol proposed by the COMS study (73) mainly because the Leiden screenings protocol is made to include patients that would be eligible for clinical EORTC vaccination or chemotherapy trials, where the COMS protocol is made as follow-up scheme for research purposes. For follow-up, the COMS study proposed annual medical examination, liver functions tests, and a chest x-ray, followed by Computer Tomography and other imaging if abnormalities are present (67). Liver imaging by abdominal ultrasound (with additional Computer Tomography imaging and fine needle aspirates when there is the slightest doubt) seems a more accurate position according to the published literature. In our view, chest x-ray is of limited use in follow-up, as already suggested in report 15 of the COMS study. We also advocate as serum screening tests S100B, LDH and γ GT, eventually in combination with alkaline phosphatase. As tumour doubling time in uveal melanoma is estimated to be 4-6 months, a semi-annual metastases screening seems advisable (22). Screening with liver ultrasound and liver function tests to detect metastases can detect

liver metastases at an asymptomatic stage in 90% of patients (10). S100B serum tests may expand this diagnosis rate to non-liver metastases. However, these tests are unable to predict metastasis at the time of enucleation.

In the near future, screening in uveal melanoma will be refined, using serum protein profile research strategies (53). Prospective studies are needed to evaluate the value of different screening serum markers and imaging techniques to detect micrometastases early.

CONCLUSION

Life-long screening for metastases in uveal melanoma patients is especially indicated in high risk patients. Although isolated liver perfusion achieved encouraging results, treatment of metastatic disease is still a major problem. Screening should consist of half-yearly serum tests, including S100, LDH and γ GT and an ultrasonography of the liver. If uncertain, it should be accompanied by Computer Tomography of the liver or fine needle biopsies. Screening of

high risk patients in combination with isolated liver perfusion chemotherapy and additional systemic chemo-immunotherapy, may improve the survival rates in uveal melanoma in patients in the near future.

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COMS study ⁷⁵	Leiden Screenings Protocol
<u>Inclusion criteria:</u> Greater than 10 mm in apical height or at least 16 mm in diameter, and those measuring between 8-10 mm in apical height that were too close to the optic nerve for optimal radiotherapy. <u>Initial metastases screening:</u> - Systemic evaluation (clinical and laboratory examination) - Chest x-ray - Liver function tests <u>Follow-up</u> - Annual follow-up - Systemic evaluation - Chest x-ray - Liver function tests <u>Additional tests if suspicion of metastases</u> - Liver ultrasound - FNAB - Liver CT	<u>Inclusion criteria (based on EORTC trials (20)):</u> Larger than 6 mm in apical height or at least 12 mm in diameter. All tumours within one disk diameter of the optic nerve. Healthy constitution of the patient; <70 years. <u>Initial metastases screening:</u> - Systemic evaluation (clinical and laboratory examination) - Chest x-ray - Liver function tests (LDH and γGT) and S100B. - Liver ultrasound <u>Follow-up</u> - semi-annual follow-up - Liver ultrasound - Liver function tests (LDH and γGT) and S100B. <u>Additional tests if suspicion of metastases</u> - Liver CT - FNAB

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