Extractions for Question: What are appropriate pre op investigations for the primary tumour?

Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS Report no. 1

Albert DM, Marcus DM.

Archives of Ophthalmology

Study Type
Cohort

Number of patients
413 eyes

Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention
histopathology

Comparators
clinical diagnosis

Follow-up

Outcomes recorded

Results
In the 3-year period of enrollment, 413 eyes with clinical diagnoses of choroidal melanoma were examined histopathologically. Four hundred eleven of these eyes were found to be diagnosed correctly*.

Misdiagnosis* rate of 0.48% - lowest ever reported.

The major challenge with regard to posterior uveal melanomas is no longer that of correct diagnosis but rather determination of the optimal treatment.

*One eye, removed after preoperative external beam radiation, was found to have a hemangioma. The second eye, removed after radioactive iodine plaque placement, was a magnocellular nevus (melanocytoma).

Additional comments on quality of study
Yes

Trends in liver function tests: A comparison with serum tumor markers in metastatic uveal melanoma (Part 2)

Hendler K, Pe’er J, Kaiserman I, Baruch R, Kalickman I, Barak V, Frenkel S,

Anticancer Research

2011

31 351 357
Abdominal ultrasonography (US) and LFTs were used to detect LM. Blood taken semi-annually liver function test (LFT) levels over consecutive visits before detection of liver metastasis (LM) from uveal melanoma (UM) with such trends in the serum tumor markers S-100beta, melanoma inhibitory activity (MIA), osteopontin (OPN), and tissue polypeptide-specific antigen (TPS). Median LFT levels were calculated at 6-month intervals prior to the clinical detection of LM. Trends in LFT levels over consecutive visits in the groups were compared with trends in the tumor markers for these groups.

AUTHORS’ CONCLUSIONS: Following the dynamics of tumor markers and LFTs may help to find metastatic disease in UM patients before the metastases are detectable by imaging, enabling earlier treatment.

Additional comments on quality of study
Unable to assess all methodological aspects from abstract, so have answered ‘not reported’ to many of the questions.
AUTHORS’ CONCLUSION: At this institute, ocular echography is more sensitive than MRI or CT for the detection of extraocular extension of choroidal malignant melanoma.

Additional comments on quality of study
Retrospective; very small sample size
Yes unable to assess all aspects of methodology from abstract. This is a retrospective study.

Grading: 3 Non-analytic studies (for example, case reports, case series)
AIM: accurate Dx of choroidal melanoma; distinguishing clinically diagnosed choroidal nevi, melanoma, and indeterminate nevomelanocytic lesions

TECHNIQUE: quantification of fundus autofluorescence in the evaluation and follow-up of choroidal nevomelanocytic tumors (digital autofluorescence and colour fundus imaging). ImageJ software.

METHODS: Retrospective; region within each lesion vs. corresponding adjacent control region

POPULATION: choroidal nevomelanocytic tumor

OUTCOME MEASURE: Index of Retinal Autofluorescence (IRA) - represent the total difference in gray-scale values between the 2 regions in each affected eye. Gray-scale intensity squared (gsi2)

RESULTS:
- 13/14 clinically diagnosed nevi = IRA <150 gsi2.
- 8/9 clinically diagnosed melanomas = IRA >150 gsi2.
- An IRA of 150 gsi2 distinguished nevi from melanomas (sensitivity 0.89, specificity 0.93).
- 15/19 pts with indeterminate nevomelanocytic lesions underwent clinical assessment and initial imaging (clinical follow-up at median 10 months).
- 3/3 pts with IRA <150 gsi2 had no evidence of clinical progression
- 6/12 lesions with IRA > 150 gsi2 had clinical progression to melanoma.
- An IRA of 150 gsi2 identifies indeterminate lesions that progress to melanoma (sens 1.0, spec 0.33)

AUTHORS’ CONCLUSIONS AND RELEVANCE Quantification of digital autofluorescence images can differentiate between clinically benign and malignant choroidal nevomelanocytic lesions and may be predictive for clinical progression of indeterminate lesions.
RESULTS:
- 2043 tumors (88%) had low to medium reflectivity (n = 1409), a mushroom shape (n = 101), or both (n = 533).
- Tumors with apical height >10 mm were more likely (P<0.001) to have a mushroom shape and less likely to have a posterior location (P<0.001) than less elevated tumors.
- 1559/1563 (99.7%) tumors judged by echography to be consistent with the diagnosis of melanoma were confirmed by pathology to be choroidal melanoma.
- For measurable extrascleral tumors <1.5 mm in height by pathology, the Echography Center graders judged extrascleral extension as possibly present in only 1/16 (6%) tumors, vs. 57% (4/7) of eyes with extrascleral extension measuring >=1.5 mm in height.

AUTHORS' CONCLUSIONS: 88% of the tumors in the COMS exhibited features characteristic for melanoma: low to medium reflectivity, the classic mushroom shape, or both. Using additional preset criteria, 96% of tumors exhibited baseline echographic characteristics consistent with the diagnosis of melanoma. Echography graders were able to detect extrascleral nodules >= 1.5 mm in elevation but not minimally elevated extraocular tumor extension. Clinicians and echographers can use these data to improve their understanding of the echographic features of untreated uveal melanomas.
2000 Screening for metastatic malignant melanoma of the uvea revisited

Eskelin S, Pyrhonen S, Summanen P, Prause JU, Kivela T.

Study Type: Diagnostic

Number of patients: 46

Study aim/Intervention: a screening study exploring role of annual USS, LFTs and CXR

Results: The sensitivity of individual LFTs ranged from 0.27 to 0.67, and their specificity from 0.90 to 0.96, with lactate dehydrogenase being the most sensitive LFT used. In 34 patients (74%; 95% CI, 59–86), metastatic uveal melanoma was diagnosed at a scheduled screening examination.

Applicable? Retrospective study. CT and MRI/PET hold greater promise but are more expensive.

Conclusions: cohort retrospective

9052 Ultrasound biomicroscopic imaging of iris melanoma: A clinicopathologic study

Giuliari GP, McGowan HD, Pavlin CJ, Heathcote JG, Simpson ER,

Study Type: Case Series

Number of patients: 14

Study aim/Intervention: INVESTIGATIONS: ultrasound biomicroscopy (UBM) features of iris melanoma with histopathology. METHODS: Retrospective analysis of medical records. POPULATION: N=14 pts that underwent surgery for iris melanoma. OUTCOMES: Clinical features, as well as the UBM findings prior to surgical intervention.
RESULTS:
- Anatomic features noted on UBM were correlated with histopathologic features seen in the surgical specimens.
- The ultrasound acoustic characteristics showed a broad spectrum of findings among iris melanomas.
- Tumor acoustic parameters correlated well with histologic features, including:
  1. tumor vascularity
  2. surface plaque
  3. extrascleral extension
  4. ciliary body involvement
  5. integrity of iris pigment epithelium.

AUTHORS’ CONCLUSIONS: UBM is a useful imaging technique for the in vivo assessment of primary iris melanoma and can provide detailed imaging of the tumor’s interface with the angle structures. The preoperative assessment of these tumors by UBM may aid the surgeon in choosing the most appropriate technique to ensure total removal.

Additional comments on quality of study

- Retrospective, very small study
- Retrospective, directly applicable population, very small sample size

7660 Whole anterior segment proton beam radiotherapy for diffuse iris melanoma 2013

Study Type
Case Series

Number of patients

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable? Conclusions

- Tx: whole anterior segment proton beam radiotherapy (PBR) to the entire iris and ciliary body
- Population: N=12 pts with Diffuse iris melanoma; mean age 57 years. Tumour iris involvement was 1-4 h (N=5 pts), 5-8 h (N=4) and 9-12 h (N=3). Angle involvement: 6-8 h (N=5 pts) and 9-12 h (N=7). Pre-Tx visual acuity (VA) = 6/5-6/6 (N=6 pts), 6/8-6/9 (N=3) and 6/18-6/38 (N=3).
- Methods: Unclear if retrospective or prospective
- Follow-up: median 3.5 years (range 1-11.6 years)

RESULTS:
- Tumour recurrence: N=0
- Glaucoma Tx required: 11/12 pts.
- Visual acuity at last follow-up: 6/5-6/9 (N=5 pts), 6/18-6/24 (N=3), 6/60-1/60 (N=2) and no light perception (N=2).
- N=4 pts developed non-severe limbal stem cell deficiency (treatable with conservative measures).

AUTHORS’ CONCLUSIONS: Whole anterior segment PBR is a useful alternative to enucleation for diffuse iris melanoma. Most patients will need treatment for glaucoma and some may require treatment for tear-film instability and/or stem cell failure.

Additional comments on quality of study

Unclear if retrospective or prospective; SMALL STUDY
Unclear if retrospective or prospective; directly applicable population, very small sample size, long follow-up.
INVESTIGATION: pre-Tx whole-body positron emission tomography (PET) imaging; received either brachytherapy using ruthenium-106 plaque, enucleation or gamma knife radiotherapy

POPULATION: Pts with choroidal melanoma.

METHODS: Retrospective review.

FOLLOW-UP: 1 year.

OUTCOMES: Metabolic activity measured as standardised uptake value (SUV).

RESULTS:
- SUV and largest basal diameter of tumour = SS correlated with metastatic death (both p=0.003).
- Inverse correlation between tumour metabolic activity and time to metastasis (p=0.049).

AUTHORS’ CONCLUSIONS: Metabolic activity by PET imaging significantly predicted the survival of patients with choroidal melanoma.

Additional comments on quality of study: Retrospective; small sample size

Features predictive of growth of choroidal nevi into melanoma.

METHODS: Retrospective medical record review

POPULATION: N= 2514 eyes with choroidal nevi; median tumor base diameter=5mm, thickness=1.5mm
RESULTS:
- Nevus growth into melanoma: 2%, 9%, and 13% of eyes (1, 5, and 10 years)
- Factors predicting growth to melanoma (multivariate):
  1. tumor thickness >2 mm (P<0.001);  2. subretinal fluid (P=0.002)
  3. symptoms (P=0.002)     4. orange pigment (P< 0.001)
  5. tumor margin within 3 mm of optic disc (P=0.001)
  6. ultrasonographic hollowness (P<0.001)     7. halo absence (P=0.009).

A mnemonic device to recall risk factors of ocular melanoma is 'To find small ocular melanoma using helpful hints,' representing thickness, fluid, symptoms, orange pigment, margin, ultrasonographic hollowness, and halo absence.
- Median hazard ratio for those with:
  1. 1 to 2 risk factors = 3.0
  2. 3 or 4 factors = 5.0
  3. 5 to 6 factors = 9.0
  4. for all 7 factors = 21.

AUTHORS' CONCLUSIONS: In an analysis of 2514 choroidal nevi, factors predictive of growth into melanoma included greater thickness, subretinal fluid, symptoms, orange pigment, margin near disc, and 2 new features: ultrasonographic hollowness and absence of halo.
- Metastases development: 35 (3%)/1329 pts.
- MULTIVARIATE Factors predictive of metastases: posterior tumor margin touching optic disc (P=0.003), documented growth (P=0.003), and greater tumor thickness (P=0.004).
- Greatest RR for metastases = tumor thickness 1.1-3.0 mm (RR 8.8) and growth (RR 3.2).

AUTHORS' CONCLUSION: Of small choroidal melanocytic tumors measuring 3 mm or less in thickness at the time of initial examination, 18% demonstrated growth and 3% metastasized during the period of follow-up. Based on this analysis, the clinical features of these tumors can be used to estimate the risk for tumor growth and metastases and assist the clinician with patient management.

Additional comments on quality of study
- Retrospective; HUGE study, unclear follow-up

1828 Iris melanoma: risk factors for metastasis in 169 consecutive patients

Study Type: Case Series
Number of patients: N=169 with microscopically confirmed iris malignant melanoma; mean age at Dx= 43 years (range, 1-90 years); mean tumor base = 6 mm (range, 1-17 mm), thickness = 2 mm (range, 1-4 mm). Extraocular extension was present in 10 eyes (6%).
Follow-up: 25 years
Tx received: Local resection (N=102 pts, 60%), enucleation (N=51, 30%), plaque radiotherapy (N=9, 5%), and observation (N=7, 4%). Metastasis developed in N=9 pts (5%).
Method: retrospective case-series; Risk factor identification of distant metastases of iris malignant melanoma.

RESULTS:
- N=1054 pts referred with suspicious tumors over a 25-year period, 169 patients (16%) had microscopically proven iris melanoma, rest (84%) had clinically diagnosed iris nevus.
- Outcome: development of distant tumor metastasis: risk of eventual metastatic spread.
- K-Meier life table analysis:
  - metastasis found in 3%, 5% and 10% at 5, 10 and 20 yrs.
- Clinical factors at initial evaluation predictive of eventual metastasis from iris melanoma included:
  - increasing age at diagnosis (P = 0.03)
  - elevated intraocular pressure (P = 0.03)
  - posterior tumor margin at angle or iris root (vs. midzone) (P = 0.02)
  - extraocular extension (P= 0.02)
  - prior surgical Tx of tumor elsewhere before referral (vs. observation) (P = 0.006).
- Method of management (resection, radiotherapy, or enucleation) had no impact on metastasis.

AUTHORS' CONCLUSIONS: Microscopically confirmed iris melanoma demonstrates distant metastasis in 5% of patients at 10 years follow-up. Metastases are more likely
to develop in those patients who are older and show tumor features of iris root/angle location with elevated intraocular pressure and extraocular extension

**Additional comments on quality of study**

Retrospective study; directly applicable population, reasonable sized study, long follow-up time.

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### Ocular Ultrasound and UBM

<table>
<thead>
<tr>
<th>Grading</th>
<th>Case-control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*</th>
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<tr>
<th>Case</th>
<th>Anterior segment imaging for iris melanocytic tumors</th>
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<thead>
<tr>
<th>Study Type</th>
<th>Diagnostic</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>61 - ASOCT was compared with UBM in 42 patients</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Inclusion/Exclusion</td>
</tr>
<tr>
<td>Study aim/Intervention</td>
<td>AS-OCT verses UBM for Melanocytic iris lesions</td>
</tr>
<tr>
<td>Comparators</td>
<td>Image quality was compared with UBM as gold standard between 2006 and 2009</td>
</tr>
<tr>
<td>Follow-up</td>
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<tr>
<td>Outcomes recorded</td>
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**Results**

AS OCT compared well with UBM in 86% of cases

But AS OCT only detected CB extension of iris melanoma in 1 of 3 cases.

**Applicable?**

Ocular Ultrasound and UBM

Retrospective comparative cohort

UBM is superior for detecting CB extension

Precise tumour measurement could be made with AS OCT to allow for radiotherapy planning

**Conclusions**

**Additional comments on quality of study**

<table>
<thead>
<tr>
<th>Case</th>
<th>PET/CT imaging: detection of choroidal melanoma</th>
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</table>
To compare uvea melanoma dimensions using PET/CT, conventional ocular ultrasound and ophthalmoscopy.

Based on AJCC classification of tumour sizes T1, T2, T3 and COMS group classification.

Smallest tumour physiologically identifiable by PET/CT had basal dimensions of 3x5.9 and an apical height of 2.9 mm. No small tumours (T1) could be detected with PET/CT.

Ocular Ultrasound and UBM

Prospective cases

Unlikely that PET/CT will be able to distinguish between naevi and melanoma.

Imaging not purely dependent on tumour size, functionally fused PET/CT was used but not all intraocular MM have SUV>2.5 some barely have any metabolic activity.

Additional comments on quality of study

**Grading:** 3  
**Non-analytic studies (for example, case reports, case series)**

<table>
<thead>
<tr>
<th>Study Type</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>50</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Study aim/Intervention</td>
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<tr>
<td>Inclusion/Exclusion</td>
<td>To compare uvea melanoma dimensions using PET/CT, conventional ocular ultrasound and ophthalmoscopy</td>
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<tr>
<td>Comparators</td>
<td>Comparative study at diagnosis Based on AJCC classification of tumour sizes T1, T2, T3 and COMS group classification</td>
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Results

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Applicable? Ocular Ultrasound and UBM

Conclusions

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Additional comments on quality of study

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<th>Study Type</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>200 - 47 (24%) had melanomas</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Study aim/Intervention</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>Compare UBM with OCT imaging to determine which is best</td>
</tr>
<tr>
<td>Comparators</td>
<td>UBM was more favorable for resolution of the posterior margin of the lesion and for structures from the pigment epithelium posteriorly, whereas AS-OCT was more favorable for anterior margin and ocular structures anterior to the IPE</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Image quality was considered good with UBM in 80%versus 68% with AS-OCT Overall, UBM was more favorable for complete tumor resolution in IPE cyst and iris melanoma</td>
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Results

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Image quality was considered good with UBM in 80%versus 68% with AS-OCT.

Overall, UBM was more favorable for complete tumor resolution in IPE cyst and iris melanoma.

Applicable? Ocular Ultrasound and UBM

Conclusions

AS-OCT suffers from optically-related image shadowing with large, pigmented, IPE and ciliary body lesions.

Advantage of AS OCT it is quick and easy to perform and not uncomfortable for the patient ( no waterbath is required) It is useful iris MM anterior to the PE for and conj tumours.
UBM is better than AS OCT for anterior segment uveal melanoma

Additional comments on quality of study

1117 Ultrasound biomicroscopy: role in diagnosis and management in 130 consecutive patients evaluated for anterior segment tumours 2005

<table>
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<tr>
<td>Diagnostic</td>
<td>130 (132 eyes) - 45 melanomas where UBM and conventional ocular ultrasound was compared. Included cysts and naevi</td>
<td>Study aim/Intervention</td>
<td>UBM and conventional ultrasound</td>
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Results
Only 29% anatomical correspondence between UBM and conventional ultrasound. For anterior segment/CB melanoma only

Applicable? Yes
Conclusions
However A/B-scan can also be used to demonstrate features characteristic of melanoma including low internal reflectivity, internal acoustic hollowness and sound attenuation, choroidal excavation, orbital shadowing and the presence of spontaneous vascular pulsations and is therefore better than UBM at diagnosis (haemangioma verses melanoma)
A/B scan (conventional US ) used for posterior melanoma and to detect posterior extension

Additional comments on quality of study

843 The use of ultrasound biomicroscopy in the evaluation of anterior segment tumors and simulating conditions 2007
Gunduz K.Hosal BM.Zilelioglu G.Gunalp I. Ophthalmologica 221 305 312
Report UBM using 50MHz probe for various anterior segment diagnoses some confirmed on histopathology

Prospective analysis of data from Aug 2002-2006
Comparison with histology where available

Ocular Ultrasound and UBM
Case series, partly comparative
Good for detecting small CB MM and to differentiate iris naevus from iris melanoma and identify pigment epithelial cysts
Useful sign loss of the acute angle shape in ring melanoma

Additional comments on quality of study

1566 Characteristic ultrasonographic findings of choroidal tumors 2003

Study Type Case Series
Number of patients
Number of patients
Results
10 choroidal melanoma described
All classic collar stud shape
50% medium reflectivity and 40% low to medium reflectivity

Applicable? Ocular Ultrasound and UBM
Conclusions
Well described B scan and A scan ultrasound characteristics can help to refine the type of intraocular tumour
Useful noninvasive investigation for choroidal tumours
Very small collection of cases from Taiwan University hospital over 4 years!

Additional comments on quality of study
**Intraocular Biopsy**

<table>
<thead>
<tr>
<th>Grading: 3</th>
<th>Non-analytic studies (for example, case reports, case series)</th>
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978  Iris ring melanoma: fine needle biopsy 2006
Char DH, Kemlitz AE, Miller T, Crawford JB.  British Journal of Ophthalmology 90 420 422

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<tr>
<td>Number of patients</td>
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<td>Study aim/Intervention</td>
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<tr>
<td>22 patients, 16 of which had FNAB to make the diagnosis</td>
<td>Biopsy performed using a transcoronal route 1800 degrees away from the tumour</td>
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<tr>
<th>Results</th>
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<tr>
<td>11 of 16 biopsies were positive</td>
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<tr>
<td>5 false negatives</td>
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<tr>
<td>Paucicellular aspirate</td>
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<tr>
<td>No cases of extra-scleral extension</td>
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<thead>
<tr>
<th>Applicable?</th>
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<tbody>
<tr>
<td>Conclusions</td>
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<tr>
<td>Intraocular Biopsy - Interventional case series</td>
</tr>
<tr>
<td>Single centre</td>
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<tr>
<td>Retrospective case not analysis</td>
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FNAB can be used to make the diagnosis of ring melanoma
None of the cases were detected with UBM or conventional ultrasound

Difficult to perform
Difficult to report
The author recommends an open biopsy when a false negative result is seen

**Additional comments on quality of study**

1722  Transvitreal fine needle aspiration biopsy: the influence of intraocular lesion size on diagnostic biopsy result 2001
Cohen VM, Dinakaran S, Parsons MA, Rennie IG.  Eye 15 2 7

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All tumour heights were recorded with A-scan ultrasonography.
This paper helps guide patients and surgeons to select which size of tumour to biopsy.

Outcome is surgeon and pathologist specific.

Results

There was insufficient material for cytological examination in 10 cases, and sufficient material in 73 cases (an overall diagnostic report rate was 88%). Yield increased significantly with increasing tumour height.

- <2 = 40%
- 2-4mm = 90%
- >4 = 98%

FNAB result correlated with pathology of enucleated specimen in 26 of 27 cases (96%) - No RD

Transient vitreous haem in 24% - No seeding

Additional comments on quality of study

Choroidal biopsies for intraocular tumors of indeterminate origin

Kvanta A, Seregard S, Kopp ED, All EC, Landau I, Berglin L.

American Journal of Ophthalmology 140 1002 1006

Diagnostic

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

10

Determine the diagnosis of a choroidal mass.

3 port pars planar vitrectomy with diamond knife incisinal biopsy of the tumour post incision diathermy

A diagnosis was achieved in all 10 patients. 5 had melanoma

Complications:

- Intraocular haemorrhage in 1 of 10 patients (one led to phthisis and loss of the eye)
- 6 eyes removed
- 2 eye suffered retinal detachment
- Very high complication rate

Specimens fixed and paraffin block sliced at 4 micrometre intervals

Retrospective, non comparative interventional case series

Exclusion criteria not reported but “case selection is important”

Useful technique but high local complication rate

Due to high risk of complications the authors suggest a needle biopsy first

Sensitivity and specificity of ultrasonography, fluorescein videoangiography, indocyanine green videoangiography, magnetic resonance and radioimmunoscintigraphy in the diagnosis of primary choroidal malignant melanoma

2195

1998
To determine the best diagnostic test for choroidal melanoma

Ultrasonography is a highly reliable diagnostic technique: sensitivity > 100%, specificity > 92%.

Comment: Conventional Ocular Ultrasound (A/B scan) is the best test to diagnose choroidal melanoma

### Results

Radioimmunoscintigraphy (sensitivity > 67%) was less sensitive than ultrasonography, MR and angiography. Specificity was good for all the considered examinations; it was 92% for ultrasonography, 87% for RIS, 83% for MR and 82% for angiography.

FV and ICFV present a high sensitivity (100%) and good specificity (82%), but these examinations cannot be used when the lesion presents a pre-equatorial localization or if opacities of dioptric media are present.

MR cannot present a very high specificity; in fact, other bulbar lesions contain paramagnetic substances with a signal similar to melanin.

Specificity of MR was 83%, because of the presence of methemoglobin, a paramagnetic substance, in 2 lesions which were false-positive. The specificity of MR was very high (100%).

### Applicable

Ultrasoundography is a highly reliable diagnostic technique: sensitivity > 100%, specificity > 92%.

[Very small number for sensitivity specificity study]

Comment: Conventional Ocular Ultrasound (A/B scan) is the best test to diagnose choroidal melanoma

### Additional comments on quality of study
Should patients be staged before primary treatment?

**Grading:** 2+  
*Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal*

| 1286 | Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23 |

**Study Type:** Diagnostic  
**Number of patients:** 2,320, 714 developed metastatic disease in the follow up period  
**Patient Characteristics**  
**Inclusion/Exclusion**  
**Study aim/Intervention**  
To report predictive value of LFTs, CXR and diagnostic imaging in the detection of metastatic disease for patients with uveal MM  
**Comparators**  
Prospective follow up with LFTs. Considered abnormal if at least twice the upper limit of normal. An abnormal result prompted MR/CT/Ultrasound or Biopsy to confirm metastatic disease.  
**Follow-up**  
Protocol: semi-annual LFTs and annual chest x-rays to screen for metastatic spread.  
**Outcomes recorded**  

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**Results**  
At least one abnormal LFT in predicting metastatic disease  
Sensitivity 14.7%  
Specificity 92.3%  
Positive predictive value 45.7%  
Negative predictive value 71.0%,

Of the LFTs, alkaline phosphatase possessed the highest diagnostic attributes.

**Applicable?**  
The benefit of annual chest x-ray is questionable based on results, in which less than 3% (297 of 11,948 x-rays performed) were abnormal. Annual screening for metastatic uveal melanoma with LFTs is warranted and that chest x-rays should be required at baseline or whenever warranted by other test results.

**Conclusions**  
Recommends serial LFTs and CXR at baseline  
LFT’s are highly specific but not sensitive in detecting metastatic disease

Comment: LFT’s are highly specific but not sensitive in detecting metastatic disease  
Cutoff level for abnormal findings of LFTs was higher than reported in both earlier studies, which may have resulted in decreased sensitivity of COMS evaluations  
Among 7,541 patients screened for COMS trials, only 70 (<1%) had metastatic melanoma detected at the time of staging.

**Additional comments on quality of study**
Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal

7480 Whole body PET/CT for initial staging of choroidal melanoma 2005
Finger PT, Kurli M, Reddy S, Tena LB, Pavlick AC. British Journal of Ophthalmology 89 1270 1274

Study Type
Diagnostic

Number of patients
52

Patient Characteristics
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Inclusion/Exclusion
To report the use of FDG/PET to stage patients with uveal melanoma
Retrospective, comparative with CT/MRI/biopsy

Applicable? Yes

Conclusions
FDG PET/CT is useful to stage patients for metastatic disease
The authors found it especially useful in the detection of extrahepatic tumours.

Results
2 of 52 (3.8%) had metastatic disease detected with PET/CT
7 of 52 (13.4%) had benign inflammatory lesions detected with PET/CT detected using known SUVs
False positive’s in 3 of 52 (6%)
LFT’s were not elevated in the two patients with metastases.

Additional comments on quality of study

Liver function tests in metastatic uveal melanoma

Kaiserman I, Amer R, Pe’er J. American Journal of Ophthalmology 137 236 243

Study Type
Diagnostic

Number of patients
30 patients with mets and 80 controls without metastases. [The controls were not matched]

Patient Characteristics
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Inclusion/Exclusion
To report the use of serial LFTs in detecting metastatic disease in follow up patients
Retrospective, comparative case control study. Measuring trend in LFT levels at 36, 24,12,6 months before and 6 months after the diagnosis of metastatic disease.

Cut off points at 60,80,100,120% of the upper limit of normal
LDH, ALK, GGT, ALT rose 6 months prior to detection of metastatic disease even though some were still within normal limits. GGT rose 3 years before detection.

LDH and ALK had the best LR six months before diagnosis. When LDH and AST rise to 80% of the upper normal limit this is suspicious whereas GGT and ALK are only suspicious when higher than upper normal limit.

Applicable? Does not answer the question - How should the patient be staged at diagnosis? But supports the measurement of LFTs at baseline.

Conclusions The authors suggest that the best screening would be LFTs combined with liver imaging.

20% of metastatic MM patients had at least one abnormal LFT when the liver ultrasound was reported as normal. This suggests that liver ultrasound is not sensitive and more detailed imaging is required.

Comment: In our experience, 40% of patients with metastatic disease confirmed with CT had normal LFTs.

Additional comments on quality of study Screening LFTs only.

Grading: 3 Non-analytic studies (for example, case reports, case series)

| 403 | Hepatic abnormalities identified on abdominal computed tomography at diagnosis of uveal melanoma | 2010 |
| Feinstein EG, Marr BP, Winston CB, Abramson DH, | Archives of Ophthalmology | 128 319 323 |

Study Type Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

AIM: Prevalence of hepatic abnormalities within 1 month of UM Dx

METHODS: Retrospective review of CT reports

POPULATION: N=91/198n pts with primary UM who had CT scan within 1 month of Dx

RESULTS:
- N=50 (55%) had ≥1 hepatic abnormalities.
- Abnormalities included:
  1. Lesions: N=38 focal (13 solitary, 25 multiple); N=15 diffuse (11 partial, 4 complete).
  2. Hepatic lesions suspected to be metastatic melanoma: N=3.
  3. Other lesions: N=39 (mainly too small to be characterized, a fatty liver, and hepatic cysts).
  4. Unclassifiable lesions: N=5/50 pts
- Lesions suspected to be metastases were more likely multiple than solitary (P=0.03).

AUTHORS’ CONCLUSION: Although hepatic abnormalities were frequently identified in patients who underwent CT within 1 month of uveal melanoma diagnosis, metastatic disease was confirmed only in the setting of multiple lesions in only a minority of patients.
Additional comments on quality of study Retrospective Retrospective, reasonable sample size, directly applicable population, follow-up N/A

2139 Predictive power of screening tests for metastasis in uveal melanoma 1998
Hicks C, Foss AJ, Hungerford JL. Eye 12 8

Study Type Diagnostic

Number of patients 245 patients

Results 55 of 245 (22%) died
Specificity and positive predictive power of abdominal ultrasound and CXR in detecting metastatic disease was 100%. But neither test is very sensitive. LFTs had a positive predictive power of <50%

Applicable? Retrospective single centre
Conclusions Did not report the incidence of metastases at diagnosis. Unclear how the sensitivity/specificity was calculated. There is no ideal staging investigation for uveal metastases. 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.

Additional comments on quality of study VICTORIA gave this study a - rating

9159 Metabolic rate of glucose (MRglu) but not standardized uptake value (SUV) can distinguish high risk from low risk uveal melanoma: Experience in 20 patients 2011

Study Type Case Series

Number of patients 20 patients

Results SCANNING: dynamic 3D 18F-FDG-PET-CT to measure metabolic rate of glucose (MRglu)
POPULATION: N=20 pts with large UM candidate for surgery; (mean age 62.4+/-14years, 16M)
METHODS: Unclear if prospective or retrospective.
RESULTS:
- All melanoma (n=20) were visualised at 18F-FDG-PET-CT.
- Mean value of tumour volume, SUVmax, SUVmean, and MRglu were: 1.15±/−1.1cc, 0.34±/−1.53, 4.08±/−1.94, and 23.73±/−14.61ml/min/100gr.
- Histopathology proved: 6 epithelioid, 7 mixed, and 7 spindle cell type.
- Epithelioid and mixed cell type showed SS >value only in MRglu parameter vs. spindle cell type.
- NS diff found btwn epithelioid and mixed cell type in volume, SUVmax, SUVmean, and MRglu values.
- Risk level: MRglu was SS lower (p<0.013) in LR (n=13) vs. HR (n=7): 29.4±/−14.2 mg/min/100gr vs 13.2±/−8.6mg/min/100gr.
- NS diff in SUV values.
- No correlation btwn SUV and MRglu, SUV and volume, and MRglu and volume.

AUTHORS’ CONCLUSIONS: 18F-FDG-PET-CT is a sensitive technique to detect large UM and dynamic acquisition allows to easily obtain MRglu. Our results show that epithelioid and mixed cell type UM both including epithelioid cells, considered at high risk, have higher glucose consumption than spindle type, without epithelioid cells and considered at low risk. This behaviour is well expressed by different values of MRglu, which gradually increase with increasing malignancy. This finding is not revealed by SUV, which is an 'estimate' of glucose consumption, but only by MRglu because it reflects the 'real' glucose consumption.

Additional comments on quality of study
- Unclear if prospective or retrospective. Very small study;
- Unclear if prospective or retrospective, Directly applicable population, very small sample size; Follow-up N/A
**What is the optimal primary treatment?**

### Grading: 1++

- High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

### Study Type

Randomised Controlled Trial

### Number of patients

1,003 patients enrolled.

### Patient Characteristics

- **Inclusion/Exclusion**

### Study aim/Intervention

- N=506 standard enucleation

### Comparators

- N=497 external radiation of the orbit and globe prior to enucleation

### Follow-up

- N=9 pts ineligible after enrollment, n=7 at interval btwn random and enucleation, n=2 after enucleation. All but n=9 pts were treated as assigned; in only 6/491 eyes treated with pre-enucleation radiation had major deviation from protocol.

### Outcomes recorded

- 5-year outcome of survival rates (known in 80% pts enrolled)

### Results

- Estimated 5-year survival rates: 57% (95% CI, 52-62%) for enuc vs. 63% (95% CI, 57-66%) for radiation+enuc.

### Applicable Conclusions

Authors’ Conclusions: No survival difference attributable to pre-enucleation radiation of large choroidal melanoma, using the COMS fractionation schedule, has been demonstrated to date in this randomized trial. The trial had statistical power of 90% to detect a relative difference in mortality rates between the two treatment arms of 20% or larger. A smaller difference is possible, but a clinically meaningful difference in mortality rates, whether from all causes or from metastatic melanoma, is unlikely.
Additional comments on quality of study

**COMS trial**

### Non-analytic studies (for example, case reports, case series)

<table>
<thead>
<tr>
<th>Grading</th>
<th>Study Type</th>
<th>Number of patients</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td><strong>3</strong></td>
<td>Case Series</td>
<td>967</td>
<td>N=58 Choroidal melanoma, median pre-op vision: 20/40 (range 20/20 to 20/400)</td>
<td>Tx: Endoresection (median 9 days) after proton beam irradiation (60 Gy applied in 4 fractions).</td>
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<td>46 95 107</td>
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</table>

**RESULTS:**
- Complications at 2 years: cataract n=21 (47%); retinal detachment n=16 (32%); secondary galucoma n=1 (3%).
- Kaplan-Meier estimates after 2 years: enucleation n=3 (8%); radiation retinopathy n=11 (28%); radiation optic neurapathy n=13 (29%); local tumour recuurence n=0; metastases n=2 (4%).
- Significant Risk factors for visual loss (multivariate): largest tumour diameter (p=0.001).
- K-M estimate for eye retention: 91.6% at 24 months.

**Additional comments on quality of study**

Prospective, directly applicable population, small study, reasonable follow-up time

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2259 2006

Adjunctive plaque radiotherapy after local resection of uveal melanoma

Damato B,

International Ophthalmology Clinics
**Results**

- **Tx:** local resection of choroidal melanomas (surgical resections were performed using a lamellar scleral flap for eye closure, hypotensive anaesthesia for haemostasis, and, in the later years, ocular decompression by pars plana vitrectomy to improve access)
- **Population:** N=163 pts (94 men, 69 women) with choroidal melanoma and a pre-op visual acuity of counting fingers or better; mean age = 50 yrs. Tumours mean diameter =13.3 mm, mean thickness = 7.4 mm. N=38 tumours extending to within 1 disc diameter (DD) of optic disc, fovea or both (that is, ‘posterior tumour extension’).
- **Follow-up:** median 28 mths (range 7 days - 18 yrs 11 mths)

**RESULTS:**
- Significant risk factors for retention of good vision - 6/12 or better (multivariate): nasal tumour location (p=0.002), and lack of posterior tumour extension (p=0.01).
- Significant risk factors for severe visual loss - hand movements or worse (multivariate): posterior tumour extension (p=0.009), male gender (p=0.05).

- **1 year post-op:**
  - all 28 pts with nasal tumours without posterior extension retained the eye, and 57% had good vision of 6/12 or better.
  - in 68 pts with temporal tumour, 90% retained the eye and preserved counting fingers or better in 82% of 56 eyes without posterior extension, and in 50% of 12 eyes with posterior extension
  - residual tumour: 32% and contributed to visual loss in 10%.
  - retinal detachment: 30% and main cause of severe visual loss in 12%.
  - cataract of any severity: 15%.
- **During the 20 year period of this study, n=13 pts did not have resection due to difficulty excising the tumour, retinal damage, and intolerance of anaesthesia. Thes pts had enucleation, plaque radiotherapy or photocoagulation instead.**

**Additional comments on quality of study**

Retrospective; good sample size, directly applicable population. Reasonable follow-up time.
RESULTS:

Preoperative factors for predicting retention of good vision (6/12 or better) (multivariate):
- nasal tumour location (p = 0.002)
- distance of >1 DD between tumour and optic disc or fovea (p = 0.010).

Most significant predictive risk factor for severe visual loss (hand movements or worse):
- posterior tumour extension to within 1 DD of optic disc and/or fovea (p = 0.009).

1 yr post-op:
- all 28 pts with nasal tumours not extending to within 1 DD of the optic disc or fovea retained the eye
  - 57% having vision of 6/12 or better
  - 93% having vision of counting fingers or better.
- In 68 pts with temporal tumours:
  - 90% retained the eye at 1 year
  - preservation of vision of counting fingers or better in 82%/56 eyes without posterior tumours extension and in 50%/12 eyes with posterior tumour extension.

AUTHORS’ CONCLUSIONS: In pts with choroidal melanoma, conservation of the eye and vision can be achieved by local resection, especially if the tumour is located nasally and does not extend close to the disc or fovea.

Additional comments on quality of study
Prospective; directly applicable population, reasonable sized study, short follow-up

839 Survival after primary enucleation for choroidal melanoma: changes induced by the introduction of conservative therapies
Gambrelle J, Grange JD, Devouassoux SM, Rivoire M, Baggetto LG, Jean LB, Fleury J, Kodjikian L.
Graefes Archive for Clinical & Experimental Ophthalmology

Study Type
Case Series

Number of patients

Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention
Comparators

Follow-up
Outcomes recorded

Applicable? Conclusions

Survival after primary enucleation for choroidal melanoma: changes induced by the introduction of conservative therapies

Study Type
Case Series

Number of patients

Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention
Comparators

Follow-up
Outcomes recorded

Applicable? Conclusions

Tx: primary enucleation with proton-beam therapy
Population: N=40 choroidal UM pts undergoing primary enucleation
Follow-up:11 years
Methods: prognostic study

RESULTS:
- 5-year melanoma-specific survival rate (K-Meier): 31.45% (SE: 7.8) after primary enucleation
- SS Prognostic factors (multivariate):
  - tumor thickness > 12 mm (p = 0.03),
  - anterior margin of tumor involving the iris (p = 0.018)
  - presence of epithelioid cells (p = 0.02).

AUTHORS’ CONCLUSIONS: The very low survival rate reported reflects the evolution of primary enucleation, which is currently indicated only for melanomas with the worst prognosis. The knowledge of current post-enucleation survival rates represents an essential achievement for both correct assessment of conservative therapies
and patient counselling

**Additional comments on quality of study**

RETROSPECTIVE, directly applicable population, fairly small size, long follow-up, no drop-outs.

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### Mortality in patients with small choroidal melanoma: COMS report no. 4

Hawkins BS, Melia M, Archives of Ophthalmology

**Study Type**: Case Series

**Number of patients**

- Patient Characteristics
- Study aim/Intervention

**Comparators**

**Follow-up**

**Outcomes recorded**

**Results**

**Applicable?**

- Tx: 8% were treated at enrollment and 33% during follow-up
- Population: N=204 pts with small choroidal melanoma (ineligible for COMS trial); small defined as 1-3.0 mm in apical height and at least 5.0 mm in basal diameter.
- Follow-up: median 92 months.

**RESULTS:**

- N=27 pts died (n=6 due to metastatic melanoma).
- 5 year all-cause mortality (K-Meier): 6.0% (95% CI 27%-9.3%)
- 8-year all-cause mortality: 14.9% (95% CI, 9.6%,-20.2%).

**AUTHORS CONCLUSIONS:** Otherwise healthy patients, average age of 60 years, without a previous diagnosis of malignant disease who have small choroidal lesions judged to be melanoma have a low risk of dying within 5 years

**Additional comments on quality of study**

COMS additional study pts with small choroidal melanoma

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### Prognostic factors for survival after enucleation for choroidal and ciliary body melanomas


**Study Type**: Case Series

**Number of patients**

- Patient Characteristics
- Study aim/Intervention

**Comparators**

**Follow-up**

**Outcomes recorded**

**Results**

**Additional comments on quality of study**

Prospective study; directly applicable population; reasonable sample size; long follow-up
Enucleation for choroidal or ciliary body melanoma

**Patient Information**
- Population: N=293 pts treated by enucleation for a choroidal or ciliary body melanoma (147 men and 146 women); median age at Tx = 61 yrs (range 26-88).
- Follow-up: median 6.2 yrs (range 21 d-43.4 yrs); median potential follow-up=25.7 yrs (range 1.9-47.7 yrs).

**Methods**
- Prognostic factors for melanoma-related death

**RESULTS**
- Increased risk of melanoma-related death (multivariate):
  - largest basal diameter (n ==264, p<0.001, mortality rate ratio (RR)=1.09 for continuous parameter in mm),
  - anterior tumour margin at iris/ciliary body vs. choroid (p<0.001, RR = 2.22)
  - non-spindle cell type vs. spindle cell (p = 0.047, RR = 1.45).
- Increased risk of death from all causes:
  - men vs. women (n=266, p=0.02, RR=1.41)
  - high age (p<0.001, RR=1.41 for continuous parameter in 10-yr age groups)
  - largest basal diameter (p<0.001, RR=1.07)
  - anterior tumour margin at iris/ciliary body (p=0.02, RR=1.52)
  - non-spindle cell type (p=0.04, RR=1.34).

**AUTHORS’ CONCLUSION**
The risk of melanoma-related death after enucleation for a choroidal or ciliary body melanoma was high for tumours with large basal diameter, non-spindle cell type and anterior location. Additional risk factors for death from all causes were male sex and high age.

**Additional comments on quality of study**
- Prospective study; directly applicable population, good sized study, long follow-up time. No drop-outs.

**Brachytherapy**

**Grading:** 2+

**Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal**

**Study Type**: Case-Control

**Number of patients**
- Cases: 294 pts.
- Controls: 294 pts.

**Comparators**
- Cases: pts with posterior UM who developed TRLE after plaque radiotherapy.
- Controls: pts with posterior UM who had not developed TRLE after plaque radiotherapy.

**Follow-up**
- Not reported in abstract

**Outcomes recorded**
- MAIN OUTCOME MEASURES: Tumor and ocular features of eyes with posterior uveal melanoma treated with plaque radiotherapy.

**Results**
- Multivariate analysis significant risk factors predictive of development of TRLE after plaque radiotherapy of posterior uveal melanoma:
  1. Bruch’s membrane rupture (P<0.001)

**Key References**
AUTHORS' CONCLUSIONS: Study identified Bruch's membrane rupture as an important factor predisposing to development of TRLE after plaque radiotherapy of posterior uveal melanoma. Other predictive factors included serous RD before radiation, large tumor basal diameter, posterior tumor location, lack of adjunctive TTT, and early increase of serous RD after plaque radiotherapy.

- Radiation dose at tumor base correlated with maximum extent of TRLE ($P = 0.003$).
- Mean interval between radiotherapy and onset of TRLE = 14 mths (median, 11 mths; range, 2-97 mths), with 88% of cases developing TRLE within 2 years of radiation.
- Mean interval between onset of TRLE and first evidence of its regression = 33 mths (median, 38 mths; range, 2-194 mths).

Additional comments on quality of study

**Conclusions**

AUTHORS' CONCLUSIONS: Study identified Bruch's membrane rupture as an important factor predisposing to development of TRLE after plaque radiotherapy of posterior uveal melanoma. Other predictive factors included serous RD before radiation, large tumor basal diameter, posterior tumor location, lack of adjunctive TTT, and early increase of serous RD after plaque radiotherapy.

Plaque radiotherapy for juxtapapillary choroidal melanoma: Tumor control in 650 consecutive cases

**Study Type**
Cohort

**Number of patients**
N=650

**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**
TTT vs. No TTT groups;
- Plaque radiotherapy using iodine-125 in 616 eyes (95%), cobalt-60 in 19 eyes (3%), iridium-192 in 12 eyes (2%), and ruthenium-106 in 3 eyes (<1%); median dose = 8000 cGy to tumor apex and adjunctive TTT was used in 307 eyes (56%)

**Follow-up**
10 years

**Outcomes recorded**
Main Outcome Measures:
Local tumor control, metastasis, and tumor-related mortality.

**Results**
Tumor recurrence, metastasis, and death: 5 yrs = 14%, 11%, and 4%, and 10 yrs = 21%, 24%, and 9%.
- Eyes treated with additional TTT showed slight (but NS) reduction in recurrence and metastasis.
- Multivariable analysis - factors predictive of tumor recurrence included: foveolar tumor requiring TTT (HR 5.07; $P<0.001$) and greater tumor thickness (HR 1.29/ mm increase; $P<0.001$).
- Factors predictive of metastasis included: greater tumor base (HR 1.21/ mm increase; $P<0.001$) and increasing intraocular pressure (HR 1.11/mmHg increase; $P= 0.020$).

**Conclusions**

AUTHORS' CONCLUSIONS: Plaque radiotherapy for juxtapapillary melanoma provides local tumor control in approximately 80% of eyes at 10 years. In subjects who received TTT, there was slight but nonsignificant improved local tumor control and lower metastatic rate.
Grading: 2- *Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

7493 Long-term outcomes of eye-conserving treatment with Ruthenium(106) brachytherapy for choroidal melanoma


Radiotherapy & Oncology

Study Type: Cohort

Number of patients: 430 patients.

Patient Characteristics

Study aim/Intervention: To evaluate long-term outcomes of eye-conserving treatment using Ruthenium-106 plaque brachytherapy with or without transpupillary thermotherapy (TTT) for small to intermediate size choroidal melanomas.

Comparators: Patients were treated according to two different protocols. Before 1997 a protocol was used combining Ru-106 brachytherapy with TTT for tumours with prominence >3 mm. From 1997 onwards, the brachytherapy dose was reduced to 400–600 Gy for combined brachytherapy and TTT. Peripheral tumours, for which TTT could not be used, were treated with doses of 600–800 Gy. TTT was generally applied 2 months after brachytherapy, and was given using an infrared diode laser, with power ranging from 500 to 1000 mW. In case of incomplete tumour regression, TTT was repeated after 6 months.

Follow-up: Median: 50 months (5 patients lost).

Outcomes recorded:

Results: Local recurrences were diagnosed in 16 patients. The actuarial 5-year local recurrence rate was 3.9% (95% CI 2.1–5.7%).

234 patients developed ocular complications, resulting in a 2-year actuarial survival rate free from complications of 49.7%, and 5-year rate of 27.8%. 194 of these 234 patients had radiation complications such as retinopathy (n = 56), maculopathy (n = 65), or opticopathy (n = 7), and combinations of these (n = 66). Forty patients had various other complications, such as vitreous haemorrhage or retinal detachment. The actuarial rates free of radiation complications were 60.0% at 2 years and 35.0% at 5 years.

Among the 391 patients with a pre-treatment visual acuity greater than 0.10, 147 had a deterioration of visual acuity in the treated eye to <0.10, thus to legal blindness. Patients with centrally or juxtapapillary located tumours had more often a poor vision before treatment, as well as greater deterioration after treatment. Actuarial rates of preserved vision greater than 0.10 were 66.9% at 2 years and 51.9% at 5 years. Actuarial rates of preserved vision greater than 0.2 reached 97.0% at 2 years and 92.0% at 5 years.
of at least 0.33 among patients with initial visual acuity of >0.32 were 55.1% at 2 years and 36.6% at 5 years. Seventeen patients eventually underwent enucleation, resulting in a 5-year actuarial enucleation rate of 4.4%. Ten patients underwent enucleation for local recurrence and seven for complications. Ocular complications necessitating enucleation were vitreous haemorrhage in three patients, serous detachment in two, neovascularisation in one, and combined vitreous haemorrhage and retinal detachment in one patient.

Significant favourable prognostic factors for preserved visual acuity of 0.33 or greater were peripheral tumour location (p = 0.02), better initial visual acuity (p < 0.001), and lower apical height (p = 0.04), while dose to sclera or apex did not have prognostic significance. Both lower apical height and better initial visual acuity remained significant when analysed separately for peripherally located tumours, while for central tumours only initial visual acuity was significant. A trend for higher rate of preserved visual acuity >0.32 was found for treatment without TTT (52.1 versus 34.5%, p = 0.06 in univariate analysis).

Prognostic factors for risk of radiation complications were younger age (p = 0.03) and use of TTT (p = 0.05), while brachytherapy dose, basal diameter and tumour location were not significantly related to risk of complications.

Additional comments on quality of study

<table>
<thead>
<tr>
<th>Grading:</th>
<th>3</th>
<th>Non-analytic studies (for example, case reports, case series)</th>
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<tbody>
<tr>
<td>390</td>
<td>Proliferative radiation retinopathy after plaque radiotherapy for uveal melanoma</td>
<td>2010</td>
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<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>Patient Characteristics</td>
</tr>
<tr>
<td>Population: N=3841 pts (N=3841 eyes) with UM</td>
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<tr>
<td>Tx: plaque radiotherapy</td>
<td>Retrospective review of medical records.</td>
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RESULTS:
- PRR development: 5.8% at 5 years, 7% at 10 and 15 years
- Mean time to onset of PRR = 32 mths (median, 30 mths; range, 4-88 mths).
- Multivariate analysis - related to the occurrence of PRR: young age (OR, 1.44; 95% CI 1.25-1.67, per decade decrease), diabetes mellitus (OR, 2.73; 95% CI, 1.69-4.40), and shorter tumor distance to the optic disc (OR, 1.10; 95% CI, 1.04-1.17).
- Most common forms of management: panretinal photocoagulation (70%), vitrectomy (21%), and observation (17%).
- Resolution of the neovascularization: 63% of eyes after Tx
AUTHORS’ CONCLUSIONS: Proliferative radiation retinopathy developed in 7% of eyes by 10 years after plaque radiotherapy for UM. The main factors for development of PRR included young age, preexistent diabetes mellitus, and shorter tumor distance to the optic disc.

Additional comments on quality of study

Good; study calls itself case control, but is not strictly this type of study

Huge study, retrospective, directly applicable population; long follow-up

Study Type: Case Series

Number of patients: 458 patients

Patient Characteristics

Inclusion/Exclusion: To determine local tumour control after ruthenium plaque radiotherapy.


Comparators: Median: 3.9 years with follow-up exceeding 1 year in 427 patients, 2 years in 364 patients, and 5 years in 153 patients, representing 93%, 81% and 53% of patients potentially having such follow-up

Follow-up: 2005 Oct 1

Outcomes recorded: There were 9 recurrences, giving actuarial rates of 1.4% at 2 years, 2.1% at 5 years and 3.3% at 7 years. Eye salvage was attempted in 8 eyes and successful in 7. The only risk factor for recurrence was large basal tumour diameter so that 8-year rates of recurrence increased from 1% to 10% if the basal tumour diameter exceeded 11 mm.

Non-comparative interventional case series. Prospective data collection. No comparison with rival technique

High rates of local tumour control can be achieved with good case selection and with techniques ensuring accurate plaque placement even without a posterior safety margin.

This case series represents favourable cases because those that were difficult to plaque accurately were treated with proton beam radiotherapy. The surgery was
performed by an experienced surgeon. Techniques have improved since this study was completed, with the design of a grooved and perforated template and the introduction of better methods of transillumination.

Additional comments on quality of study

1129 Visual acuity after Ruthenium(106) brachytherapy of choroidal melanomas 2005 Oct 1
Damato B, Patel I, Campbell IR, Mayles HM, Errington RD, International Journal of Radiation Oncology, Biology, Physics 63 392 400

Study Type: Case Series

Number of patients: 458 patients

Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention
To determine visual outcome after ruthenium plaque radiotherapy.

Comparators

Follow-up
Follow-up exceeded 1 year in 427 patients, 2 years in 364 and 5 years in 153.

Outcomes recorded

Results
In 344 patients with 6/12 or better vision, such vision was conserved in 80% of patients at 2 years, 67% at 5 years and 55% at 9 years. Factors associated with visual loss were posterior tumour extent, increased tumour thickness, temporal tumour location and older age. The six-year actuarial rates of loss of 6/12 vision were approximately 1%, 21%, 50% and 80% according to the number of these risk factors, in 60, 138, 106 and 40 patients respectively. Results are also given for retention of 6/60 vision and Counting Fingers.

The recurrence rate was 2%.

Applicable? Rates of ocular conservation are reported according to risk factors. This study drew attention to the toxic tumour syndrome, which causes visual loss even when optic disc and fovea do not receive much radiation.

Conclusions A limitation of this study is that many patients were followed up at their own hospital where measurement of visual acuity may not have been performed accurately. Another limitation is that patients who were unlikely to do well with ruthenium plaque radiotherapy were treated with other methods, such as proton beam radiotherapy or local resection.

Additional comments on quality of study

329 Strabismus in adults with uveal melanoma following episcleral plaque brachytherapy 2007
Study Type: Case Series

Results

- Tx: plaque brachytherapy and its subsequent treatment. Commonest radionuclide isotope used: Ru-106 (13 eyes, 81%) and N=3 eyes received I-125 (19%). Size of plaque = 20 mm in most (8 eyes, 62%), 15 mm used in 5 eyes (38%). Radiation dose to apex: median 100 gray (range 80-120). Median duration of plaque brachytherapy application = 76 hours (range 36-140).
- POPULATON: N=16 adult pts with malignant melanoma of the uveal tract. Site of tumor: N=7 (44%) peripheral choroid, N=7 (44%) posterior pole choroid, N=1 (6%) peripapillary choroid, N=1 (6%) iris melanoma.
- METHODS: Retrospective review of case notes (single centre)

RESULTS:
- Final visual acuity of 20/200: N=5 cases (33%).
- N=16 pts (1.7%) with treated UM developed persistent diplopia or strabismus.
- ONSET: in 1st yr (N=11 patients, 69%); 2nd yr (N=2, 13%); yrs 5, 7 and 8 (N=1 each, 6% each).
- N=2 (13%) did not require any intervention.
- N=14 (88%) required treatment: n=7 (50%) prisms only, n=3 (21%) botulinum toxin (BTXA) injections, n=4 (29%) extraocular muscle surgery (n=3 required one operation, n=1 required 2).

AUTHORS’ CONCLUSIONS: The incidence of ocular motility disorders following plaque brachytherapy in our cohort was 1.7% over 8 years and we include this in the consent process for conservative treatment of intraocular tumors. Options for treatment for persistent diplopia or strabismus include prisms, botulinum toxin injection, or surgery

Additional comments on quality of study
Good
Retrospective, small study; directly applicable population; long follow-up.

Study Type: Case Series

Results

- Tx: 103Pd (seeds equivalent to 125I) ophthalmic plaque brachytherapy; mean apical radiation dose of 80.5 Gy during 5-7 days' continuous treatment
- Population: N=100 intraocular melanoma, negative for metastatic disease
- Follow-up: mean 4.6 years (55.4 months)

RESULTS:
AUTHORS’ CONCLUSION: Long-term results now exist describing the use of 103Pd plaque radiotherapy for uveal (iris, ciliary body, and choroidal) melanoma. Compared with the results from centers using 125I, patients in this series experienced equivalent local control rates and better visual function.

Additional comments on quality of study

BERTIL COMMENT: Good

RETROSPECTIVE, directly applicable population, reasonable size, long follow-up

RESULTS:
- Cataract in pre-Tx phakic pts: N=82/350 (23%).
- Radiation maculopathy: 58 (14%); both radiation maculopathy and optic neuropathy: 23 (6%).
- Radiation optic neuropathy without evidence of maculopathy: N=0
- In N=9 pts (2%), radiation retinopathy could not be assessed because of either dense cataract (n=5) or persistent vitreous hemorrhage (n=4).
- Local control rate: 96.7%.
- Life table analysis visual acuity: 79% and 69% of pts with 20/200 or better before treatment (n = 357) are expected to retain that acuity for 5 and 10 years.
- Life table analysis: probability that 92.7% and 86.6% of pts will be free of metastatic disease at 5 and 10 years.

CONCLUSIONS: In this series of 400 patients with UM, results after (103)Pd ophthalmic plaque radiotherapy were superior to those reported for alternative forms of radiation.
RESULTS:
- Tumour control: 97.1% (4.6 yrs)
- Reduction in mean height; o: 55.1%
- Recurrence: 2.9% of pts
- Visual acuity: maintained in 16.2%, increased in 17.6%.
- Complications: 33% had retinopathy and 14.6% optic neuropathy.
- Enucleation due to complications: N=5
- Melanoma-related death: N=1

AUTHORS' CONCLUSIONS: I-125 EB is effective in tumour control, allowing preservation of the eye and useful visual function for the majority of patients.
The plaque size was selected to be 2 mm larger than the base of the entire intraocular and extraocular tumor on all margins. The radioisotope used for plaque radiotherapy was iodine-125 in 12 cases, cobalt-60 in four cases, and iridium-192 in one case.

In conclusion, small and medium-size ciliary body and choroidal melanoma with a clinically visible extraocular extension less than 3 mm in thickness can, in selected cases, be treated with plaque radiotherapy.

Additionally, the extraocular extension was anterior and visible under the conjunctiva by external examination. In 10 of 14 patients who had the anterior extraocular extension visible clinically, the extraocular extension decreased in basal diameter and the scleral fibers gradually appeared through the regressed mass. The scleral integrity was preserved in all cases, with no obvious clinical sign of necrosis. The final visual acuity was better than 20/40 in five (29%) eyes and better than 20/200 in 10 (59%) eyes. Radiation complications included posterior subcapsular cataract that developed in seven eyes (41%), neovascular glaucoma in two (12%), retinopathy in two (12%), and vitreous hemorrhage in two (12%). In no case was enucleation performed for tumor recurrence or radiation complications.

Applicable? In conclusion, small and medium-size ciliary body and choroidal melanoma with a clinically visible extraocular extension less than 3 mm in thickness can, in selected cases, be treated with plaque radiotherapy.

Additional comments on quality of study

Study Type

Comparison

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

To study visual outcome, local tumour control and eye preservation five years after ruthenium plaque radiotherapy for choroidal melanoma.

Comparators

Treatment dose was 100 Gy to 6mm with a plaque at least 4 mm larger than the largest basal tumour diameter.

Follow-up

Outcomes recorded

Results

The five-year probability for not losing at least 5 Snellen lines was 59% and for retaining pre-operative visual acuity of 0.33 or better was 28%.

Local recurrence occurred in 15 patients (27%) at five years. Risk factors were anterior location, large basal diameter and thickness exceeding 8mm.

Enucleation was performed in 28% eyes at 5 years.

Applicable? Ruthenium plaque radiotherapy can be regarded as a good treatment option for small and medium sized tumours but not for large tumours.

Conclusions

Additional comments on quality of study
Excluded ciliary body involvement; insufficient follow-up; adjuvant laser therapy. All tumours received at least a 2 mm safety margin. Median: 33 months.

Tumours that are close to the fovea in young patients appear more likely to show local recurrence. Tumour height >5 mm was the only prognostic factor that determined lack of response. These results may be used to select which tumours require adjuvant therapy.

**Study Type** Case Series

**Number of patients** 189 patients

**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention** Excluded ciliary body involvement; insufficient follow-up; adjuvant laser therapy. All tumours received at least a 2 mm safety margin.

**Comparators**

**Follow-up** Median: 33 months.

**Outcomes recorded**

**Results** Fourteen of 189 patients recurred and 13 of 189 patients did not respond within the first year from treatment. Univariate evaluation of clinical factors related to the risk of local recurrence revealed an association of decreasing hazard with increasing age (HR per year increase 0.96; 95% CI 0.92 to 0.99; p=0.019) and with increasing distance from the fovea (HR 0.71; 95% CI 0.51 to 0.98; p=0.038). There was a greater hazard of recurrence in patients with pre-treatment subfoveal fluid than without (p=0.03, HR 3.25) and evidence of increasing hazard with increasing basal diameter (p=0.032, HR 1.25). Subsequent Cox stepwise analysis, including all variables (except plaque type shape, which was collinear with location), confirmed the association with age (p=0.096, adjusted HR 0.043) and proximity to the fovea (p=0.04, adjusted HR 0.069). Univariate logistic regression (table 3) looking at the same set of factors associated with non-response showed evidence of association with tumour height (p=0.006, OR 1.55). Successive multiple variable logistic regression (table 3), confirmed that the only factor associated with the likelihood of non-response was the height of the tumour (p=0.027, OR 1.52). 27% of tumours had a thickness of greater than 5 mm and the median tumour height in the non-response group was 5.6 mm, while in the recurrence group it was 4.9 mm.

**Applicable?** Tumours that are close to the fovea in young patients appear more likely to show local recurrence. Tumour height >5 mm was the only prognostic factor that determined lack of response. These results may be used to select which tumours require adjuvant therapy.

**Conclusions**

**Additional comments on quality of study**

8901 Tumour regression after brachytherapy for uveal melanoma: Lack of association with survival 2012

Rashid MM, Kivela T. Acta Ophthalmologica Conference 90
**Study Type**: Case Series

**Number of patients**: 270 patients

**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

**Results**

The final visual acuity was 20/20 to 20/50 in 37% of eyes, 20/60 to 20/100 in 16% and 20/200 to no light perception (including enucleation) in 46% of eyes.

Local tumour recurrence developed in 5 eyes and was located at the posterior tumour margin in all cases. Using Kaplan-Meier, this equated to less than 1% at 1 year, 2% at 2 years, 3% at 3 years and 3% at 5 years. Univariate analysis indicated that recurrence was associated with tumour epicenter at macula, diffuse tumour shape, and tumour extending under foveola. The Kaplan-Meier, 5-year rates of complications were retinopathy (39%), maculopathy (18%), papillopathy (38%), extramacular...
Plaque radiotherapy combined with transpupillary thermotherapy provides excellent local tumor control with only 3% recurrence at 5 years' follow-up.

Applicable? Yes

Conclusions

Additional comments on quality of study

1946 Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients


Study Type: Case Series

Number of patients: 1106

Patient Characteristics

Inclusion/Exclusion: To identify clinical predictive factors for visual outcome in a large series of patients who underwent plaque radiotherapy for uveal melanoma.

Study aim/Intervention: Not given.

Comparators: The radioisotope used in the plaque was iodine 125 in 649 patients (59%), ruthenium 106 in 60 (5%), cobalt 60 in 300 (27%), and iridium 192 in 97 (9%). Radioisotopes that are no longer used (e.g., cobalt) were used.

Follow-up: Not given.

Outcomes recorded: Not given.

Results

On multivariable analysis, the best combination of factors related to poor visual acuity outcome (20/200 to no light perception) were patient age of 60 years or older, poor initial visual acuity, increasing tumor thickness, proximity to foveola less than 5 mm, anterior tumor margin posterior to the equator, presence of subretinal fluid, radioactive isotope (ruthenium, cobalt, and iridium), notched plaque shape, and tumor recurrence.

Using Kaplan-Meier estimates, 3% of patients had poor visual acuity at 1 year, 34% at 5 years, 68% at 10 years, and 87% at 15 years. When evaluating final visual acuity as a function of tumor thickness using Kaplan-Meier estimates, eyes with a small melanoma demonstrated poor vision in less than 1% of patients at 1 year, 24% at 5 years, and 60% at 10 years. Eyes with a medium melanoma demonstrated poor vision in 3% of patients at 1 year, 31% at 5 years, and 69% at 10 years. Eyes with a large melanoma displayed poor vision in 8% of patients at 1 year and 64% at 5 years (too few patients were available for a reliable 10-year estimate). Analysis of the combined effects of the predictive factors at the time of treatment revealed ultimate poor visual acuity in 19% of patients with no risk factors and in a mean of 39% of patients with 1 factor, 49% with 2 factors, 58% with 3 factors, 64% with 4 factors, and 50% with 5 factors.

Applicable? Yes

Conclusions

The subset of patients with hope for long-term good vision after plaque radiotherapy for choroidal melanoma include younger patients with small tumors at sites remote from the optic disc and foveola. It is important for all patients treated with plaque radiotherapy for choroidal melanoma to realize that the globe is usually salvaged, in 94% of cases, 27 using this organ-sparing technique, but the visual function of the eye is limited and ultimate visual outcome is generally poor. The visual outcome is very poor.

Additional comments on quality of study

Brachytherapy - Iodine
The Collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: IV. Ten-year mortality findings and prognostic factors. COMS report number 24

Collaborative Ocular Melanoma Study Group

American Journal of Ophthalmology

2004

Study Type
Randomised Controlled Trial

Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention
Pre-enucleation radiation

Comparators
Enucleation alone

Follow-up
At least 5 years and up to 10 years after treatment

Outcomes recorded
death and related outcomes (see below)

Results
Death within 10 years: N=576/1,003 pts died. - - - - - - - - - - - - - - - - - - - - - - - 10-year all-cause mortality: 61% (both Tx arms). - - - - - - - - - - 10-year rates of death with histopathologically confirmed melanoma metastasis: 45% (RAD) vs. 40% (ENUC). - - - Primary predictors of time to all-cause death and death with melanoma metastasis: older age and larger maximum basal tumor diameter. - - - - No diff in unadjusted or adjusted mortality rates between Tx arms. - - - - 145/448 pts (32%) eligible for 10yrs follow-up = Alive and clinically cancer-free 10 years after Tx.

Applicable?
Yes

Conclusions
AUTHORS' CONCLUSIONS: Longer follow-up confirmed the earlier report of no survival advantage attributable to pre-enucleation radiation. Mortality rates by baseline characteristics should facilitate counseling of patients who have large choroidal melanoma and no evidence of metastasis or another malignancy at diagnosis

Additional comments on quality of study
COMS study

The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28

Collaborative Ocular Melanoma Study Group, Archives of Ophthalmology
2006

Study Type
Randomised Controlled Trial

Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention
Iodine 125 ((125)I) brachytherapy

Comparators
Enucleation

Follow-up
5 to 15 years: 12 year results.

Outcomes recorded
MAIN OUTCOME MEASURES: Deaths from all causes and deaths with histopathologically confirmed melanoma metastasis.
AUTHORS' CONCLUSION: Longer follow-up of patients confirmed the earlier report of no survival differences between patients whose tumors were treated with (125)I brachytherapy and those treated with enucleation. APPLICATION TO CLINICAL PRACTICE: Estimated mortality rates by baseline characteristics should facilitate counseling of patients who have choroidal melanoma of a size and in a location suitable for enucleation or (125)I brachytherapy and no evidence of metastasis or another malignancy.

Additional comments on quality of study

Part of COMS study

The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report no. 28

Hawkins BS. Archives of Ophthalmology

Results

12 years post-Tx: N=231 (45%) alive and clinically cancer free
- 5- and 10-year all-cause mortality: 19% (BRACHY) and 35% (ENUC); by 12 years = 43% and 41%
with histopath melanoma metastasis: 10%, 18%, and 21 (BRACHY), and 11%, 17%, and 17% (ENUC)
Primary predictors of time to death from all causes and death with melanoma metastasis = Older age and larger maximum basal tumor diameter.

Applicable? Yes

Conclusions

AUTHORS' CONCLUSION: Longer follow-up of patients confirmed the earlier report of no survival differences between patients whose tumors were treated with (125)I brachytherapy and those treated with enucleation. APPLICATION TO CLINICAL PRACTICE: Estimated mortality rates by baseline characteristics should facilitate counseling of patients who have choroidal melanoma of a size and in a location suitable for enucleation or (125)I brachytherapy and no evidence of metastasis or another malignancy.

Additional comments on quality of study

Very good

The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: Initial mortality findings: COMS report no. 18
### Study Type
Randomised Controlled Trial

### Number of patients
**Patient Characteristics**  **Inclusion/Exclusion**  **Study aim/Intervention**  **Comparators**  **Follow-up**  **Outcomes recorded**

<table>
<thead>
<tr>
<th>1317 patients enrolled (660 enucleation vs. 657 brachytherapy)</th>
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</table>

### Results
- Adherence: 91% of patients treated per protocol.
- Mortality: N=364 (n=188, 28% in enucleation arm and n=176, 27% in brachytherapy arm.
- Unadjusted estimated 5-yr survival rates: 81% and 82% (NS difference between groups overall, P = .48).
- Adjusted estimated risk ratio for $^{125}$I brachytherapy vs enucleation: 0.99 (95% CI 0.80-1.22).
- Five-year rates of death with histopathologically confirmed melanoma metastasis: 11% and 9% (adjusted estimated risk ratio: 0.91, 95% CI, 0.66-1.24)

### Applicable?
Yes.

### Conclusions
Conclusions: Mortality rates following $^{125}$I brachytherapy did not differ from mortality rates following enucleation for up to 12 years after treatment of patients with choroidal melanoma who enrolled in this COMS trial. The power of the study was sufficient to indicate that neither treatment is likely to increase or decrease mortality rates by as much as 25% relative to the other.

### Additional comments on quality of study
Very Good

### Study Type
Randomised Controlled Trial

### Number of patients
**Patient Characteristics**  **Inclusion/Exclusion**  **Study aim/Intervention**  **Comparators**  **Follow-up**  **Outcomes recorded**

<table>
<thead>
<tr>
<th>650 patients.</th>
</tr>
</thead>
</table>

### Study aim/Intervention
To determine rates of local tumour recurrence and enucleation after iodine-125 brachytherapy.

### Comparators
enucleation

### Follow-up
11 1/2-year accrual period

### Outcomes recorded
See below
the radiation dose was prescribed to the apex of the tumor. For tumors 2.5 to 4.9 mm in apical height, the prescription point was 5 mm from the interior surface of the sclera.

Results

By 5 years after enrollment, 10.3% of plaqued eyes (95% confidence interval [CI], 8.0–13.2%) exhibited treatment failure. The 5-year cumulative risk of enucleation in this cohort was slightly higher: 12.5% (95% CI, 10.0–15.6%). In multivariate analysis of baseline predictors of time to reported treatment failure (Table 6), only older age at time of enrollment, greater apical height, and proximity to the FAZ were associated independently with treatment failure. The risk in persons over age 50 was nearly three times as high as in those less than 50 years of age. Risk factors for enucleation were evaluated separately. Univariate predictors of enucleation (P < 0.05) within 5 years (Table 7) included male gender, greater apical height of the tumor, longer basal dimension, poorer visual acuity in the tumor-containing eye at baseline, collar-button tumor shape, presence of retinal detachment over the tumor, lower radiation dose to the tumor apex, and higher dose to the sclera. Distance to the FAZ was marginally associated with enucleation (P = 0.15). In multivariate analysis adjusting for univariate predictors of enucleation, only apical height of the tumor, poorer baseline visual acuity in the tumor-containing eye, and distance between the proximal tumor border and the FAZ were independent predictors of outcome, although gender bordered on statistical significance. Treatment failure, which was strongly associated with reduced survival in the univariate model (risk ratio, 1.9; P < 0.01), was only weakly associated after adjusting for other baseline variables (adjusted risk ratio, 1.5; P = 0.08; 95% CI, 0.94–2.52).

Conclusions

The findings show low risk of local treatment failure or secondary enucleation after definitive I125 brachytherapy for choroidal melanoma. Whether the rate of local treatment failure is ‘low’ is debatable. No comment about about whether recurrence was central or marginal.

Many surgeons were inexperienced.

If tumour proximity to FAZ is a risk factor for recurrence, this is probably because of inadequate plaque placement.

The data are probably not sufficient to determine whether local tumour recurrence contributed to mortality, especially if treatment failure is likely to be lethal only with small tumours.

Additional comments on quality of study

Very Good GET I-125 DATA TO ADD TO RESULTS

AUTHORS’ CONCLUSIONS: Local treatment failure and enucleation were relatively infrequent events after I(125) brachytherapy within the COMS. Tx failure typically occurred early and was associated weakly with poorer survival. The COMS randomized trial documented the absence of a clinically or statistically significant difference in survival for patients randomly assigned to enucleation versus brachytherapy. This analysis documents the efficacy of brachytherapy to achieve sustained local tumor control and to conserve the globe.

1789 Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16 2001
This report describes visual acuity outcomes and baseline and treatment factors associated with maintenance or loss of visual acuity during the first 3 years after treatment.

The size of the plaque used for I125 brachytherapy was chosen so that the tumor base, with a tumor-free margin of 2 to 3 mm on all borders, was covered entirely by the plaque. An exception was made for tumors within 2 mm of the optic nerve; a notched or trimmed plaque with its edge placed between the margin of the tumor and the optic nerve could be used for these cases. For tumors 5.0 mm or more in apical height, the radiation dose was prescribed to the apex of the tumor. For tumors 2.5 to 4.9 mm in apical height, the prescription point was 5 mm from the interior surface of the sclera.

Visual acuity was measured by a COMS-certified examiner according to a standard protocol that used best refractive correction and a Bailey-Lovie chart.

86% had visual acuity measurements at 42 months.

Summary, visual acuity during the first 3 years after I125 plaque radiotherapy for choroidal melanoma declined at a rate of approximately two lines per year on average, although this time course was highly variable from patient to patient. Forty-three to 49% of treated eyes had substantial impairment in visual acuity by 3 years after treatment, defined as a loss of six or more lines of visual acuity from the pretreatment level (49% of eyes) or a decrease in visual acuity from better than 20/200 at baseline to 20/200 or worse during follow-up (43% of eyes). Thirty-nine percent of eyes had visual acuity within three lines of baseline at the 3-year follow-up examination. By 3 years after treatment, 13% of eyes had visual acuity three to six lines less than baseline, whereas 3% had visual acuity three or more lines more than baseline. The large subgroup of patients with no high risk characteristics, that is, patients without diabetes with dome-shaped tumors 5.0 mm or less in apical height that were more than 2.0 mm away from the FAZ and did not have retinal detachment, maintained on average 20/40 or better visual acuity throughout the 3-year follow-up.

**Study Type**
Randomised Controlled Trial

**Number of patients**
623 patients.

**Patient Characteristics**
Inclusion/Exclusion

**Study aim/Intervention**

**Comparators**

**Follow-up**
86% had visual acuity measurements at 42 months.

**Outcomes recorded**

**Results**
1. Both groups: at 6 months had increased difficulty with driving, near activities, and activities using stereopsis or binocularity and decreased levels of anxiety at the 6-month follow-up. No change in depression. BRACHY had smaller decrease in peripheral vision score. BRACHY group developed more new cancers and more new health conditions during follow-up than ENUC group.
2. BRACHY SS better than ENUC for: ADVS night driving and NEI-VFQ driving scales. Tx diff diminished over follow-up and was NS for later follow-up times; VFQ peripheral vision scale, vision-dependent social function,
3. NS difference between groups for: near vision activities or activities using stereopsis or binocularity, % pts night driving, % pts who stopped driving due to vision (through the 5 years), depression, HADS anxiety (although better with enucleation), SF-36 scores (physical and mental)
4. MULTIVARIATE: ENUC: SS better day driving by 5 years (but NS btwn groups at other times); BRACHY SS better SF-36 mental and physical; higher but NS deaths in BRACHY vs. enuc.; NS diff in anxiety measures.

**Conclusions**

Applicable?
period. In these patients, the probability of losing six or more lines within 3 years was 12%, and the probability of 20/200 or worse visual acuity was 9%. However, 32% of eyes in this favorable subgroup had a three-line or more decrease in visual acuity that was confirmed at the next follow-up examination within the 3 years of follow-up.

High risk characteristics were: tumor height >5.0 mm, distance between tumor and foveal avascular zone <2.0 mm, diabetes, non-dome-shaped tumor, and presence of tumor-associated retinal detachment.

**Additional comments on quality of study**

NOTE TO RACHEL - NEED TO EXTRACT ABOUT IODINE

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**Grading:**

1+ **Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**

<table>
<thead>
<tr>
<th>1760</th>
<th>The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, II: Characteristics of patients enrolled and not enrolled: COMS report no. 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Archives of Ophthalmology</td>
<td>119 951 965</td>
</tr>
</tbody>
</table>

**Study Type:** Randomised Controlled Trial

**Number of patients**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
</tr>
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</table>

**Results**

This paper gives pt characteristics only for the COMS trial.

Methods: All pts diagnosed with choroidal melanoma and evaluated for the clinical trial at COMS centers from November 1986 through July 31, 1998. Results: Of 8712 patients with choroidal melanoma, 5046 had tumors of eligible size; of these: 2882 (57%) were eligible for enrollment, and 1317 (46% of eligible patients, 26% of patients with tumors of eligible size) enrolled. Most differences btwn eligible and ineligible pts corresponded to eligibility and exclusion criteria. However, ineligible patients were older and had thicker tumors (vs. eligible pts). Eligible pts who enrolled were slightly older and had larger tumors (vs. those who did not enroll). 48% of enrolled pts had choroidal melanoma with the apex located temporal to the fovea (vs. 40% of eligible pts not enrolled vs. 25% of ineligible patients).

**Applicable?**

Authors’ Conclusions: This trial was designed to yield internally valid treatment comparisons through random assignment to treatment at time of enrollment. Information from this and other studies document that enrolled patients were similar to other patients with choroidal melanoma who were treated with brachytherapy. These findings support the external validity of the trial and applicability of treatment findings to all patients who meet the criteria used to judge eligibility for the trial.

**Additional comments on quality of study**

COMS data - details of trial pts only, not results

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**8884** Long-term update on prospective, randomized trial: Charged particles versus iodine-125 plaque therapy in the management of uveal melanoma

Helium ion (charged particle) therapy (minimum tumor dose of 70 GyE delivered to tumor apex in 5 fx over 7-11 days).

Iodine-125 plaque therapy (minimum tumor dose of 70 GyE delivered to tumor apex in majority in 4 days [range, 3-7 days]).

Median follow-up for the helium and iodine arm is 14.6 years and 12.3 years, respectively (p = 0.22), and for those alive, 18.3 and 16.8 years (p = 0.81).

Long-term clinical outcome was evaluated using Cox's regression model for univariate and multivariate analyses, as well as the log-rank test to compare subsets.

AUTHORS' CONCLUSIONS: Charged particle therapy results in significantly higher LC and eye retention rates compared with plaque therapy in this trial. The data presented here are consistent with other long-term plaque data (see COMS trials 10 and 12 year updates). Treatment with particles is the most important predictor of higher LC and eye preservation. This is the only long-term data available to date from a randomized study comparing radiation modalities in uveal melanoma therapy, and confirms significant clinical benefit with charged particle therapy.
### Study Type

#### Number of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=94 pts (N=30 brachytherapy, N=64 stereotactic radiotherapy).</td>
<td>(125)Iodine brachytherapy vs. stereotactic radiotherapy</td>
<td>Median follow-up = 46 months in both cohorts.</td>
<td>Outcomes included: rates postradiotherapy local recurrence, secondary enucleation, metastasis and radiotherapy complications. Kaplan-Meier estimates were used to determine the actuarial rates, and logrank test to compare between the estimates.</td>
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</table>

### Results

**BRACHY vs. STEREO**
- Tumour recurrence (50 mths, actuarial rates): 11% and 7% (p=0.61)
- Secondary enucleation: 11% and 21% (p=0.30)
- Metastasis: 4% and 16% (p=0.11).
- Tx complications (50 mths, actuarial rates): cataracts = 62% and 75% (p=0.1); neovascular glaucoma = 8% and 47% (p=0.002); radiation retinopathy = 59% and 89% (p=0.0001); radiation papillopathy = 39% and 74% (p=0.003).

### Applicable? Conclusions

| Yes. |

**AUTHORS’ CONCLUSIONS:** Both (125)iodine brachytherapy and stereotactic radiotherapy demonstrate comparable efficacy in the management of juxtapapillary choroidal melanoma. However, stereotactic radiotherapy shows statistically significant higher radiation-induced ocular morbidities at 4 years postradiotherapy.

### Additional comments on quality of study

- retrospective

**Generally ok**

### Study Type

#### Number of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
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<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>AS FOR ID 9117</td>
<td>AS FOR ID 9117</td>
<td>Iodine-125 brachytherapy cases were modeled with plaque simulator software for dosimetric analysis. Mean doses at predetermined intraocular points were recalculated. Kaplan-Meier estimates determined the actuarial rates of late toxicities, and</td>
<td>Iodine-125 brachytherapy vs. stereotactic radiotherapy</td>
<td>Median follow-up = 46 months in both cohorts.</td>
</tr>
</tbody>
</table>
The log-rank test compared the estimates.

**Results**

- Radiation toxicity rates (IBT vs SRT at 50 mths): cataracts of 62% and 75% (P=.1), for neovascular glaucoma 8% and 47% (P=.002), for radiation retinopathy 59% and 89% (P=.0001), and for radiation papillopathy 39% and 74% (P=.003).

- Dosimetric comparisons (IBT vs. SRT) - mean doses:
  1. Lens centre: 12.8 and 14.1 Gy (P=.56)
  2. Lens posterior pole: 17.6 and 19.7 Gy (P=.44)
  3. Ciliary body: 13.9 and 10.8 Gy (P=.30)
  4. Optic disc centre: 61.9 and 69.7 Gy (P=.03)
  5. Retina at 5-mm distance from tumor margin: 48.9 and 60.1 Gy (P<.0001).

**Applicable? Conclusions**

Yes

**AUTHORS’ CONCLUSIONS:** Late radiation-induced toxicities were greater with SRT, which is secondary to the high-dose exposure inherent to the technique as compared with IBT. When technically feasible, IBT is preferred to treat juxtapapillary choroidal melanoma.

**Additional comments on quality of study**

Good - retrospective (Same trial as RID 9117)

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**Study Type:** Cohort

**Number of patients**

N=95 (n=55 grp1, n=40 grp2)

**Patient Characteristics**

**Inclusion/Exclusion**

GROUP 1: radioactive iodine-125 ((125)I): 85Gy to the apical height of the tumor

GROUP 2: radioactive iodine-125 ((125)I): 85Gy to a prescription point of 5.0mm

**Study aim/Intervention**

- GROUP 1: radioactive iodine-125 ((125)I): 85Gy to the apical height of the tumor
- GROUP 2: radioactive iodine-125 ((125)I): 85Gy to a prescription point of 5.0mm

**Comparators**

Not reported

**Follow-up**

See below

**Outcomes recorded**

---

**Results**

INCIDENCE RATE OF SPECIFIC COMPLICATIONS:

- Gp 2 had SS > incidence of radiation retinopathy, radiation optic neuropathy, and/or visually significant cataract formation than group 1 (P = 0.028).

**Applicable? Conclusions**

AUTHORS’ CONCLUSION: Treatment of choroidal melanomas less than 5mm in apical height with (125)I brachytherapy to the true apical height is equally effective when compared to treatment with 85Gy to 5.0mm. Treatment to the apical height of the tumor may result in lower incidence of radiation-related complications

**Additional comments on quality of study**

Retrospective

Unable to determine all aspects of methodology from abstract, have thus answered 'not reported' for many of the questions.
iodine 125 plaque brachytherapy (IBT); mean dose to apex=87 Gy, noncollimated 20-25-mm plaques

Follow-up: 5 years

study aim/intervention

Comparators

Outcomes recorded

PARTICIPANTS

N=97 IBT / 121 pts, large UM (COMS criteria); median tumor height = 10.7

AUTHORS’ CONCLUSIONS: Iodine 125 plaque brachytherapy seems to be a safe and effective alternative to enucleation with regard to survival and local tumor control. It provides a fair chance of preserving the eye with acceptable cosmesis and a reasonable chance of conserving useful vision for 1 to 2 years.

Additionally, retrospective case control study - but results only given for the IBT group.

Retroactive study; directly applicable population, reasonable sized study, long follow-up time.

Study Type: Case-Control

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

IBT

Tx = 97, Non-IBT

Tx = 24

RESULTS (ONLY GIVEN FOR THE IBT GROUP):

- All-cause and melanoma-specific survival at 5 yrs: 62% (95% CI 49%-72%) and 65% (95% CI 52%-75%).
- Local tumor recurrence at 5 yrs: 6% (95% CI, 2%-14%).
- Major cosmetic abnormality was 38% (95% CI, 26%-52%).
- Median visual acuity: 20/100 at baseline and 20/1600 at 2 yrs post-Tx.
- Avoiding low vision and blindness at 2 yrs: 11% (95% CI, 4%-24%) and 26% (95% CI 16%-37%).
- Best predictors of visual loss: tumor height and location entirely posterior to the ora serrata.
- 49 person-years without low vision (median, 0.6 yrs; range 0.04-8.2) and 111 person-years without blindness (median 1.0 yrs; range 0.03-8.6) in the treated eye were conserved.

Applicable? Yes

Conclusions

Tx: iodine 125 plaque brachytherapy (IBT); mean dose to apex=87 Gy, noncollimated 20-25-mm plaques

Population: N=97 IBT / 121 pts, large UM (COMS criteria); median tumor height = 10.7

AUTHORS’ CONCLUSIONS: Iodine 125 plaque brachytherapy seems to be a safe and effective alternative to enucleation with regard to survival and local tumor control. It provides a fair chance of preserving the eye with acceptable cosmesis and a reasonable chance of conserving useful vision for 1 to 2 years.

Additional comments on quality of study

Retrospective study; directly applicable population, reasonable sized study, long follow-up time.

Study Type: Cohort

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

N=14 (I), N=12 (RU)

Iodine 125 (I125) plaque radiotherapy; dose of 85 Gy at tumour apex

Ruthenium 106 (Ru106) plaque +/ Transpupillary thermotherapy plaque; dose of 100 Gy at tumour apex

Mean follow was 24.2 months (range 14.3-38.7) in I group; and 30.2 months (range 7.6-48.3) in RU

treatment complications and tumor control: radiation maculopathy, enucleation, local tumor recurrence, and metastasis.
AUTHORS' CONCLUSIONS: The management of choroidal melanoma with a thickness of 5-7 mm is controversial. Iodine seems to provide higher local tumor control, while Ruthenium induces less radiation complications. Although there are several limitations to our study, we found that I125 represents a better option in this subgroup of tumors, especially for preventing metastatic disease.

Treatment with I125 resulted in:
- higher rate of radiation maculopathy (14.3% vs 8.3%)
- lower rate of enucleation (7.1% vs 8.3%)
- lower rate of tumor recurrence (7.1% vs 8.3%)
- lower rate of metastasis (0% vs 25%).
- The differences were NS (univariate), except for metastasis rate.
- Mean interval between Tx and onset of metastatic disease = 30.5 months.

Applicable? Yes

AUTHORS’ CONCLUSIONS: The management of choroidal melanoma with a thickness of 5-7 mm is controversial. Iodine seems to provide higher local tumor control, while Ruthenium induces less radiation complications. Although there are several limitations to our study, we found that I125 represents a better option in this subgroup of tumors, especially for preventing metastatic disease.

Additional comments on quality of study
Retrospective; small study
Info from abstract so unable to assess all methodological aspects, thus have answered 'not reported' to a number of the questions.

Grading: 3 Non-analytic studies (for example, case reports, case series)

8965 I-125 episcleral plaque brachytherapy for uveal melanoma: A 15-year single institution experience 2012

Study Type Case Series
Patient Characteristics Study aim/Intervention Comparators Follow-up Outcomes recorded

Results

Applicable? Yes

Tx: I-125 episcleral plaque brachytherapy
Population: UM (N=494)
Rv of medical records and follow-up records (Median follow-up: 42 mths; range 6-175 mths)

RESULTS:
- Mean tumor thickness and long basal diameter = 4.9 mm and 12.1 mm.
- Median plaque size = 18 mm.
- N = 110 plaques (22.6%) required notch (as near optic nerve)
- Estimated 5-year overall survival = 73.2%
- Estimated 5 year cause-specific survivals = 88.6%
- Local control = 95.3% (N=26 local failures, and N=56 pts (11.3%) developed metastatic disease).
- Mean dose to tumor = similar in those with local control vs. those with local failures (269.1 Gy vs. 261.7 Gy; p = 0.74).
- N=38 pts (6.8%) had enucleation. Reasons = local recurrence (n=20), 2nd primary tumor (n=1) and severe radiation toxicity (n=17; 3% of treated patients).
- Mean dose to tumor base in patients requiring enucleation = SS > those without enucleation (323.3 Gy vs. 263.5 Gy, p = 0.02).
- There was no significant association between presence of a notch or size of the plaque and recurrence or enucleation (all p > 0.05).

AUTHORS' CONCLUSIONS: I-125 episcleral plaque brachytherapy leads to excellent local control and globe preservation. There is no association between need for a notched plaque or plaque size with tumor recurrence or need for enucleation. Patients requiring enucleation had higher a radiation dose to the base of the tumor.

Incidence and treatment of toxicity following 125I episcleral plaque brachytherapy for uveal melanoma


Study Type: Case Series

RESULTS:
- Mean tumor thickness and long basal diameter = 5.0 mm and 12.1 mm
- Median plaque size = 18 mm.
- N=114 plaques (24.3%) required a notch (as near optic nerve).
- Median visual acuity in the affected eye: Pre-Tx = 20/40, at most recent followup = 20/150.
- 3-year rates of radiation retinopathy, radiation papillopathy, and exudative retinal detachment were 45% (n=162), 14% (n=47), and 10% (n=41).
- 3-year rates of cystoid macular edema, vitreous hemorrhage, and enucleation due to radiation toxicity were 17% (n=61), 12% (n=47), and 4% (n=14).
- 3-year rates of cataract formation, neovascularization of the iris and neovascular glaucoma were 29% (n=115), 6% (n=24), and 4% (n=16).
- N=29 pts (6.2%) received intravitreal triamcinolone acetonide for Tx of cystoid macular edema
- N=32 pts (6.8%) received subtenons triamcinolone acetonide injections for Tx of cystoid macular edema or radiation retinopathy.
- Starting in 2005, N=71 (15.1%) pts began receiving intravitreal bevacizumab for Tx of cystoid macular edema, neovascularization of the iris, or neovascular glaucoma.
- Pts having plaque brachytherapy after 2005 = SS less likely to need enucleation due to radiation toxicity vs.pts undergoing plaque brachytherapy prior to 2005 (p = 0.01).

AUTHORS' CONCLUSIONS: Radiation retinopathy and cataract formation are common toxicities 3 yrs following I plaque brachytherapy for UM. Pts treated after 2005 were SSy less likely to require an enucleation due to toxicity than patients treated prior to 2005, possibly due to the use of bevacizumab.

Additional comments on quality of study Good Large study; directly applicable population (UM); long follow-up
RESULTS:
- N=11/996 had late intraocular recurrence >5 yrs (5.5-15.3 yrs) post-Tx (All 11 had had Iodine 125 ((125)I) brachytherapy).
- These pts did not have either high-risk clinical parameters (thin, posterior tumors in proximity to the optic nerve) or radiation dosimetry characteristics (low dose-delivery radiation) associated with a known increased risk for tumor recurrence after radioactive plaques.
- Annualized incidence rate for regrowth = 1.9% per year (btwn 5 - 15 years post-Iodine Tx).
- In contrast to charged particle radiation, the risk of late recurrence after (125)I brachytherapy continued with increased follow-up.

AUTHORS' CONCLUSIONS: There was a significantly higher late recurrence rate with (125)I brachytherapy vs. charged particle radiation. Although tumor enlargement 5 or more years after radiation can be the result of intratumor hemorrhage, in a patient treated with radioactive plaque, a late failure is a distinct possibility.

Additional comments on quality of study
- Good - data from 3 studies combined for this Case-series: data taken from pts in 3 x randomised case-series; very large study; directly applicable population; long follow-up

2111 Ten-year follow-up of helium ion therapy for uveal melanoma 1998
Char DH, Kroll SM, Castro J. American Journal of Ophthalmology 125 81 89

Study Type Case Series
Number of patients Patient Characteristics Study aim/Intervention
Inclusion/Exclusion
Comparators
Follow-up
Outcomes recorded

Results
Applicable? Yes
Conclusions
- Tx: helium ion radiation
- Population: N=218 pts (218 eyes) with UM
- Methods: Retrospective review
- Follow-up: 10 years

1592 Late radiation failures after iodine 125 brachytherapy for uveal melanoma compared with charged-particle (proton or helium ion) therapy 2002
Char DH, Kroll S, Phillips TL, Quivey JM. Ophthalmology 109 1850 1854

Study Type Case Series
Number of patients Patient Characteristics Study aim/Intervention
Inclusion/Exclusion
Comparators
Follow-up
Outcomes recorded

Results
Applicable? Yes
Conclusions
- Tx: radiation therapy
- Data from 3 phase I, II and II trials (partially randomised case-series)
- RESULTS:
  - N=11/996 had late intraocular recurrence >5 yrs (5.5-15.3 yrs) post-Tx (All 11 had had Iodine 125 ((125)I) brachytherapy).
  - These pts did not have either high-risk clinical parameters (thin, posterior tumors in proximity to the optic nerve) or radiation dosimetry characteristics (low dose-delivery radiation) associated with a known increased risk for tumor recurrence after radioactive plaques.
  - Annualized incidence rate for regrowth = 1.9% per year (btwn 5 - 15 years post-Iodine Tx).
  - In contrast to charged particle radiation, the risk of late recurrence after (125)I brachytherapy continued with increased follow-up.

AUTHORS' CONCLUSIONS: There was a significantly higher late recurrence rate with (125)I brachytherapy vs. charged particle radiation. Although tumor enlargement 5 or more years after radiation can be the result of intratumor hemorrhage, in a patient treated with radioactive plaque, a late failure is a distinct possibility.

Additional comments on quality of study
- Good - data from 3 studies combined for this Case-series: data taken from pts in 3 x randomised case-series; very large study; directly applicable population; long follow-up
RESULTS:
- Local tumor control: N=208/218 eyes (95.4%)  
- Enucleation (10 yrs): 46/218 eyes (22.4%) - most due to anterior ocular segment complications.  
- Mortality (10 yrs): 102/218 pts (46.8%); N=51 non-melanoma-related deaths and N=51 due to metastatic melanoma.  
- Best-corrected visual acuity (>20/40) in N=21/93 eyes (23%) of pts who were alive and who had retained their eyes >or=10yrs post-Tx.  
- In pts with tumors <6 mm in height and >3 mm from nerve or the fovea, 13/18 (72%) retained visual acuity >20/40.  
- In pts with thicker tumors or those close to nerve or fovea, only 11% retained >20/40 acuity.  

AUTHORS’ CONCLUSIONS: Helium ion irradiation of uveal melanoma is associated with good local tumor control and reasonable retention of the treated eye 10 years after treatment. In eyes with tumors less than 6 mm in thickness and more than 3 mm distant from the optic nerve and fovea, many retain excellent vision.

Additional comments on quality of study: Retrospective, directly applicable population, large study, long follow-up.

8817 Treating medium-sized choroidal melanomas with eye plaque brachytherapy (125-I) 2012

RESULTS:
- N=10 developed metastasis.  
- 70% pts had 2 year and 45% had 3 yr follow-up.  
- Local failure at 3 yrs: 3% of eyes vs. 10.3% in CMS plaques.  
- Late radiation side effects: retinopathy (18/60), cataracts (20/60), and optic neuropathy (10/ 60).  
- Vision in affected eye: preserved in 28/43 (65%) at 2 yrs and 7% had vision improvement.  
- 28% had worse vision at 2 yrs (COMS = 49%).

CONCLUSION: Use of the plaques was associated with fewer local recurrences than reported with the COMS plaques. The plaque planning software and design of the plaques produced clinical results, which compared favorably to the COMS data. There was an equivalent distant metastasis rate of 10% in both series suggesting that the likelihood of metastatic spread is an inherent feature of the melanoma and not related to treatment technique. Radiation related late side effects are similar to the COMS data. However, preliminary results suggested that vision preservation was better with the eye plaques (28% had worsened vision in our study as compared with 49% of COMS patients). Future studies and larger numbers of patients will be required to confirm the low tumor recurrence rates and the encouraging visual outcomes.
Management of iris melanomas with 125Iodine plaque radiotherapy


Study Type: Case Series

Results:

TX: (125)Iodine plaque brachytherapy
Population: N=14 pts, iris melanoma (IM); blue/green irises. Mean largest basal dimension and thickness = 7.1 +/- 2.1 mm (range, 4.0 to 11.5 mm) and 2.2 +/- 0.8 mm (range, 1.0 to 3.5 mm), respectively. N=10 pts (71%) had seeding and n=2 (14%) had glaucoma at presentation.
Follow-up: Retrospective study - median 26.6 +/- 19.5 mths (range, 6 to 72 mths)

RESULTS:
- Tumor control: 100%
- Enucleation due to radiation-induced complications: 0%
- At last visit 100% pts alive and free of metastasis.
- Final visual acuity: same as or better than pre-Tx in N= 9 patients (75%).
- Most common complications: Cataract (n=8; 75%), persistent glaucoma (n=2; 17%) and anterior uveitis (1; 8%). No other significant complication was seen during the follow-up period.

AUTHORS’ CONCLUSIONS: Plaque radiotherapy is a safe and effective conservative treatment option for IM, although cataract is a common, yet treatable, complication. This treatment scheme circumvents an intraocular procedure and may avoid the dissemination of malignant cells, and provides a margin of safety in the treatment of clinically undetectable disease.

Additional comments on quality of study: Good

RETROSPECTIVE, directly applicable population, very small study (but IM is not so common), long follow-up

2722 Treatment of choroidal melanoma with I-125 plaque


Study Type: Case Series

Results:

TX: I-125 plaque.

Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Applicable? Conclusions

Good
RETROSPECTIVE, directly applicable population, very small study (but IM is not so common), long follow-up
**Applicable?**

**Conclusions**

Tx: high activity I-125 episcleral plaque therapy; apical doses range 74.25 - 83.66 Gy; scleral doses ranged 41 to 160 Gy.

Population: N=144 OM pts. Tumor volumes: range =14 to 3449 mm³; lesion size included small (n = 15; height < 5 mm, and/or largest basal diameter of 8-16 mm) and large (n = 45; height > 8 mm, and/or largest basal diameter > 16 mm).

Follow-up: range 25-90 mths (median 46 mths).

RESULTS:
- Ocular survival: n=130/144.
- Reasons for enucleation: progressive tumor growth (n=4), extrascleral extension (n=4), or blind/painful eye (n=6).
- Complications (n=94): cataract (n=43), optic neuropathy (n=12), neovascular glaucoma (n=8) and retinopathies (n=31).
- Visual acuity: pre-Tx = 102 pts with 20/200 vision; at last follow-up = 59 pts with 20/200 or better.

AUTHORS’ CONCLUSION: The use of episcleral I-125 plaque therapy allows for safe and effective therapy in patients with ocular melanoma of various size depending on location and probable visual acuity outcome. A total apical dose of 75 Gy given at 60-65 cGy/hour provides durable local control with acceptable complication rates

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**Results**

**Applicable?**

**Conclusions**

Tx: 125I plaque brachytherapy (COMS design)

Population: N=156 OM

Follow-up: median 6.2 yrs

RESULTS:
- AT 5 YEARS
  - Overall survival: 83%.
  - Disease-specific survival: 91%.
  - Initial local control: 92%.
  - Ultimate local control after secondary therapy: 100% (including 9 enucleations).
  - Risk of metastasis: 10% at 5 yrs, 27% at 10 yrs.
  - Vision (same or improved): 25% pts (44% pts maintained visual acuity >20/200).
  - Chronic pain or discomfort in treated eye: 13% pts.
  - Dose rates to the tumor apex >90 to 100 cGy/h were associated with increased systemic control but worse radiation toxicity.

AUTHORS’ CONCLUSION: Patients in our series experienced excellent local tumor control. Higher dose rates to the tumor apex were associated with reduced rates of
### Additional comments on quality of study

Good

**RETROSPECTIVE, directly applicable population, reasonable sized study, long follow-up**

### Study Type

Case Series

### Number of patients

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### Results

- **Tx:** N=56 I-125 brachytherapy, N=52 enucleated, N=3 received no Tx.
- **Population:** N=111, posterior UM
- **Methods:** Rev of clinical records
- **Follow-up:** median 36 mths (mean 52 mths; range 2 mths to 13 yrs)

**RESULTS:**

- Annual age-adjusted incidence (per million population) of posterior UM: 8.5 for women and 8.9 for men.
- Enucleation: BRACHY n=4 (n=2 for tumour recurrence, n=2 for neovascular glaucoma).
- Visual acuity of 0.1 or better: retained 40% (87% had it pre-Tx) after median 61 mths.
- 5- and 10-year melanoma-specific mortality rates: BRACHY = 13.4 and 23.8%; ENUC = 49.5 and 49.5%.

**AUTHORS’ CONCLUSION:** After brachytherapy, many patients lost useful vision due to radiation-induced complications. The probability of retaining the eye was high and only two patients experienced recurrent tumour growth. The mortality rates compare well with published series, and the differences in tumour size explain the difference in mortality between the two treatment groups.

### Additional comments on quality of study

Retrospective; directly applicable population, reasonable sized study, long follow-up

### Study Type

Case Series

### Number of patients

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### Results

- **1342** 125I plaque brachytherapy for anterior uveal melanomas
- **Lumbroso LR, Charif CM, Levy C, Plancher C, Dendale R, Asselain B, Solignac S, Mazal A, Desjardins L.**
- **Eye**
- **2004**
- **Number of patients:** 18
- **Follow-up:** 911
- **Outcomes recorded:** 916
RESULTS:
- Overall 5-year survival rate: 88.3%
- 5-year metastasis rate: 4%
- Local recurrence rate: 1.5%
- Mean final visual acuity: 20/40.
- Most frequent ocular complications at 5 yrs: cataract (50.3%), maculopathy (18.3%), intraocular inflammation (19.3%), and glaucoma (10.6%). Optic neuropathy, retinal detachment, keratitis, and intravitreous haemorrhage were also described.
- Risk factors for worse survival: age >65 years and initial tumour thickness >4 mm.
- Risk factors for cataract development: age >65 years, male gender, and tumour diameter >10mm.
- Risk factors for intraocular inflammation: tumour thickness > 4 mm and invasion of the ciliary body.

AUTHORS’ CONCLUSIONS: The use of 125I plaque brachytherapy to treat melanomas situated anterior to the equator allows good local and systemic control with a low rate of macular and optic disc complications. The most frequent complication was cataract formation.

Additional comments on quality of study
Retrospective; directly applicable population, reasonable sized study, long follow-up

1052 Quality of life after iodine 125 brachytherapy vs enucleation for choroidal melanoma: 5-year results from the Collaborative Ocular Melanoma Study: COMS QOLS Report No. 3
Archives Ophthalmology 124 226 238

Study Type
Case Series

Number of patients

Results

Applicable? Yes

Conclusions

Tx: 125I plaque brachytherapy vs enucleation for choroidal melanoma
Pts: N=209, OM with medium-sized tumors
Methods: telephne interview with subgroup of pts from COMS RCT who were followed up prospectively. SF-36, Activities of Daily Vision Scale, the National Eye Institute Visual Function Questionnaire, and the Hospital Anxiety and Depression Scale and additional questions..

RESULTS:
- Significant increase in both Tx groups in levels of reported difficulty for most vision-oriented activities, and in bodily and ocular pain, 6 mths post-Tx.
- Differences in visual function btwn Tx = small, but significant favoring brachytherapy (for driving during 1st year of follow-up, and for peripheral vision during 1st 2 years of follow-up).
- Anxiety levels: significant decrease in both groups post-Tx, but brachytherapy pts with symptoms of anxiety were less likely to report later resolution of symptoms than patients with symptoms of anxiety who were treated with enucleation.
- Impact of Tx on satisfaction with appearance and concern about cancer recurrence: no treatment-related differences at 2 years and later follow-up times (unable to assess at 1 year).

AUTHORS’ CONCLUSIONS: Patients treated with brachytherapy reported significantly better visual function than patients treated with enucleation with respect to driving and peripheral vision for up to 2 years following treatment. Differences between treatments in visual function diminished by 3 to 5 years posttreatment, paralleling decline in visual acuity in brachytherapy-treated eyes. Patients treated with brachytherapy were more likely to have symptoms of anxiety during follow-up than patients treated with enucleation. APPLICATION TO CLINICAL PRACTICE: Given that no significant differences in survival between enucleation and brachytherapy have been found, the differences demonstrated here for driving and anxiety will allow the individual patient and physician to make informed choices regarding treatment based on personal preferences.

Additional comments on quality of study
- Subset of pts from COMS
- Prospective (observational data in ancillary study of COMS RCT, using a subset of pts); unable to determine from abstract if data collected in equal pts from each RTx group and if randomisation was preserved. Directly applicable population, large study, long follow-up time.

Study Type
- Case Series

Number of patients
- Patient Characteristics
- Inclusion/Exclusion

Study aim/Intervention
- Comparators

Follow-up
- Outcomes recorded

Applicable?
- Conclusions

Results

Tx: iodine 125 plaque brachytherapy (IBT); primary IBT (median dose to tumor apex, 87 Gy).
Population: N= 96 pts with large UM (according to COMS criteria); median tumor height and diameter = 10.7 mm (range 4.5-16.8) and 16.5 mm (range 7.3-25.0)
Methods: retrospective nonrandomized interventional study.
Follow-up: median 3.5 years (range 0.3-10.4).

RESULTS:
- persistent (RD).
- 5-year cumulative incidences: cataract = 69% (95% CI 57%-78%), iris neovascularization 62% (95% CI,50%-71%), glaucoma = 60% (95% CI 48%-70%)
- Posterior segment complications were less common.
- 5-year incidence: maculopathy = 52% (95% CI 35%-65%) and optic neuropathy= 46% (95 CI, 30%-61%); vitreous hemorrhage = 36% (95 CI, 23%-48%) and persistent exudative retinal detachment = 25% (95 CI, 15%-36%).
- >80% of complications were Dx within 3 yrs. Cataract was the earliest complication to appear.
- Cumulative incidence of dying without developing a complication (except for cataract): 0.24 to 0.62 times that of first developing the complication.
- Increasing tumor height, which correlated to increasing doses to adjacent tissues, was associated with time to cataract (P = 0.017), iris neovascularization (P = 0.087), and exudative retinal detachment (P = 0.046).
- Maculopathy and optic neuropathy were associated primarily with distance to the fovea (P = 0.015) and optic disc (P = 0.015), respectively.
- 47% of 57 pts with cataract underwent cataract extraction
- 12% of 51 pts with glaucoma were treated with cyclophotocoagulation.
- 5-year prevalences of cataract, elevated intraocular pressure, and exudative retinal detachment = 43%, 39%, and 13%.
CONCLUSIONS: The frequency with which ocular complications develop after IBT is notably influenced by competing risks. Cumulative incidence and prevalence analysis provide realistic estimates for patient counseling.

### Additional comments on quality of study
- Retrospective; Directly applicable population; reasonable sample size; reasonably long follow-up

### Study Type
- Case Series

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<th>Number of patients</th>
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<tbody>
<tr>
<td>1670</td>
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<td>Plaque radiotherapy for large posterior uveal melanomas (&gt; or =8-mm thick) in 354 consecutive patients</td>
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### Study
- Tx: plaque radiotherapy
- POPULATION: N=354 Pts with large posterior UM measuring 8 mm or greater in thickness.
- METHODS: Prospective
- FOLLOW-UP: 10 years

**Results**
- Final visual acuity = poor in 57% at 5 years and 89% at 10 years.
- MULTIVARIATE: Most important risk factors for poor visual acuity included - retinal invasion by melanoma, increasing patient age, iodine 125 (I(125)) isotope, and <2 mm distance to the optic disc. Treatment-related complications at 5 years included proliferative retinopathy (25%), maculopathy (24%), papillopathy (22%), cataract (66%), neovascular glaucoma (21%), vitreous hemorrhage (23%), and scleral necrosis (7%).
- Enucleation: 24% at 5 years and 34% at 10 years
- MULTIVARIATE: risk factors for enucleation included - left eye, peripheral tumor margin anterior rather than posterior to the equator, increasing tumor thickness, and ruthenium 106 (Ru(106)) isotope.
- Local tumor recurrence: 9% at 5 years and 13% at 10 years.
- MULTIVARIATE: risk factors for tumor recurrence included - Ru(106) radioisotope and ciliary body involvement with tumor.
- Tumor-related metastase: 30% at 5 years and 55% at 10 years.
- MULTIVARIATE: risk factors for metastases included - inferotemporal meridian, anterior extension of the tumor to the iris root, increasing tumor base, and posterior margin < 2 mm from the optic nerve.

**AUTHORS’ CONCLUSIONS:** Plaque radiotherapy provided tumor control at 10 years in 87% of patients with selected large posterior uveal melanomas (>8 mm thick) that otherwise would have been managed with enucleation. The large intraocular mass and associated features and radiation complications led to poor visual acuity in most patients. At 10 years follow-up, enucleation was necessary in 34% of patients, and metastasis developed in 55% of patients.

### Additional comments on quality of study
- Prospective; Directly applicable population; large study; long follow-up

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1241     New Zealand experience of I125 brachytherapy for choroidal melanoma     2005
**Results**

**Applicable? Conclusions**

Tx: I125 brachytherapy

Pts: N=92 pts with choroidal melanoma (92% had complete follow-up data); Average pre-Tx tumour dimensions = 3.9 mm (thickness) and 15.2 mm (diameter).

RESULTS:
- Regression of tumour: 88%
- Enucleation: N=5
- Melanoma-related deaths: N=5
- Visual acuity remained: >6/12 (35% pts) and >6/60 (51% pts).
- Most frequently observed complication: radiation retinopathy (maculopathy 23%, peripheral retinopathy 17%).
- Radiation cataract: 11%; optic neuropathy 10%.
- Dose >90 Gy to macula = 63% chance of developing maculopathy (P < 0.01).
- Tumour >4 mm significantly increased risk of radiation maculopathy (P = 0.003).
- Development of radiation cataract = dose-related; >25 Gy to lens = 44% risk of cataract(P<0.001).
- Risk of optic neuropathy: 50% for tumours <4 mm from disc margin (P < 0.001).

CONCLUSIONS: Patient outcomes following brachytherapy were excellent with a high percentage of patients retaining mobility vision. Development of complications was related to the tumour location and dose to non-tumour structures.

**Additional comments on quality of study**

unclear follow-up

Prospective study; directly applicable population, reasonably sized study, unclear follow-up time.

**Episceral plaque 125I brachytherapy for choroidal melanoma: A single institution retrospective review**

Vonk DT, Gordon JD, Javid C, Stea B, Brachytherapy Conference 12

**Results**

Episceral plaque brachytherapy represents a standard treatment for appropriate choroidal melanoma patients. Variations in prescription dose and dose-rate exist for reasons of physician preference and logistics. Materials and Methods: A retrospective chart review of all patients treated with I plaque brachytherapy for ocular melanoma at the University of Arizona was performed. A total of 140 patient records were the basis for this analysis. Data was obtained on dose and dose-rate to the tumor and sensitive structures. Patients were followed by the treating ocular oncologist for local tumor control, distant metastases, and preservation of vision. Results: The current series represents a similar patient population to those reported by COMS. Prescription dose varied compared to COMS with tumors less than 5mm thick prescribed to the tumor apex
rather than to 5mm. The change in prescription point allowed for reduced irradiation of sensitive structures without loss of tumor control. Additionally, the current series varies from ABS recommendations in regards to dose-rate. Current guidelines recommend the dose rate at the prescription point to range between 60 cGy/hr and 105 cGy/hr. This series included patients with a dose-rate as low as 50.6 cGy/hr. No correlation was found between lower dose-rate and tumor control. Conclusions: The results of this retrospective single institution review confirm what has been known for 3 decades from the COMS study that <sup>125</sup>I episcleral plaque therapy is an effective, low morbidity, treatment for medium size and small but rapidly growing choroidal melanomas. For tumors with a thickness less than 5mm, reducing the prescription depth to the tumor apex served to decrease the dose to all sensitive structures within the eye. This dose reduction occurred without any significant loss of local control. Although our dose-rate varied somewhat from the ABS guidelines no differences in either the control or the complications rates were noted as a function of dose-rate

**Applicable?**

- Tx: 125I plaque brachytherapy (dose varied compared to COMS: tumors <5mm thick prescribed to the tumor apex rather than to 5mm). This allowed for reduced irradiation of sensitive structures without loss of tumor control. This series included patients with a dose-rate as low as 50.6 cGy/hr.
- Population: N=140, OM pts (similar to COMS pts)
- Methods: Retrospective chart review
- Follow-up:

**RESULTS:**

- No correlation found between lower dose-rate and tumor control.

**AUTHORS’ CONCLUSIONS:** The results of this retrospective single institution review confirm what has been known for 3 decades from the COMS study that <sup>125</sup>I episcleral plaque therapy is an effective, low morbidity, treatment for medium size and small but rapidly growing choroidal melanomas. For tumors with a thickness less than 5mm, reducing the prescription depth to the tumor apex served to decrease the dose to all sensitive structures within the eye. This dose reduction occurred without any significant loss of local control. Although our dose-rate varied somewhat from the ABS guidelines no differences in either the control or the complications rates were noted as a function of dose-rate

**Additional comments on quality of study**

- Retrospective; unclear follow-up time
- Retrospective study; directly applicable population, reasonably sized study, UNCLEAR follow-up time.

---

**Brachytherapy - Ruthenium**

**Grading:** 1+

**Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>Case series</td>
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</table>

**Study Type**

- Metaanalysis

**Patient Characteristics**

- Long-term survival after ruthenium plaque radiotherapy for uveal melanoma. A meta-analysis of studies including 1,066 patients

**Study aim/Intervention**

- 1999

**Comparators**

- Seregard S.

**Follow-up**

- Acta Ophthalmologica Scandinavica

**Outcomes recorded**

- 77 414 417
RESULTS:
- 5-year melanoma-related mortality rate: 6% for small and medium tumours (T1/T2) and 26% for large (T3) tumours.
- 5- and 10-year melanoma-related mortality rates for a balanced set of tumours with small, medium and large tumours being present in similar proportions were 14% and 22%.

AUTHORS' CONCLUSION: Case series of patients with uveal melanoma managed by brachytherapy may be pooled to increase sample size and study power. The present estimate of survival following ruthenium plaque radiotherapy compares favourably with previously summarised data of survival after enucleation for similarly sized tumours.
Combination Tx: ruthenium brachytherapy (BT) simultaneously with transpupillary thermotherapy (TTT)

**Main outcome measures** were rate of tumor regression, recurrences, enucleations, metastases, recurrence-free and overall survival rate, and visual acuity, assessed by Kaplan-Meier analysis.

**AUTHORS’ CONCLUSION:** Combined treatment of choroidal melanoma with ruthenium BT and simultaneous TTT seems to provide higher local control, eye-globe preservation, and recurrence-free survival rates than treatment with BT alone and results in similar rates of metastases and overall survival.

---

### Results

- BT+TTT vs. BT resulted in:
  - higher rate of tumor regression (63% vs. 49%, p=0.036)
  - lower 5-year tumor recurrence rate (96% vs. 83%, p<0.034)
  - higher eye-globe preservation (98% vs. 87%, p<0.024)
  - higher recurrence-free survival rates (89% vs. 67%, p<0.017)
  - NS diff in complications (p>0.5), metastasis-free (93% vs. 81%, p>0.22), overall survival rates (91% vs. 81%, p>0.39), or in visual outcomes.

---

### Applicable? 
**YES**

**Conclusions**

Authors’ conclusion: Combined treatment of choroidal melanoma with ruthenium BT and simultaneous TTT seems to provide higher local control, eye-globe preservation, and recurrence-free survival rates than treatment with BT alone and results in similar rates of metastases and overall survival.

---

**Additional comments on quality of study**

Retrospective Info from abstract so unable to assess all methodological aspects, thus have answered 'not reported' to a number of the questions.
Ruthenium brachytherapy (BT) + simultaneous transpupillary thermotherapy (TTT) vs. BT alone. 5 years main outcome measures were rate of tumor regression, recurrences, enucleations, metastases, recurrence-free and overall survival rate, and visual acuity, assessed by Kaplan-Meier analysis.

**AUTHORS’ CONCLUSIONS:** Combined Tx of choroidal melanoma with ruthenium BT and simultaneous TTT seems to provide higher local control, eye-globe preservation, and recurrence-free survival rates than treatment with BT alone and results in similar rates of metastases and overall survival.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Cohort</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>Patient Characteristics</td>
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<td>N=133 (BT+ TTT) N=63; BT N=7</td>
<td>Study aim/Intervention</td>
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<tr>
<td></td>
<td>Ruthenium brachytherapy (BT) + simultaneous transpupillary thermotherapy (TTT)</td>
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<td></td>
<td>Comparators</td>
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<td>BT alone.</td>
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<td>5 years</td>
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</table>

**Results**
- Tumour regression: SS higher in BT + TTT (63% vs. 49%, p=0.036) vs. BT alone.
- 5-year tumour recurrence rate: SS lower in BT + TTT (96% vs. 83%, p<0.034)
- Eye-globe preservation: SS higher in BT + TTT (98% vs. 87%, p<0.024)
- Recurrence-free survival rates: SS higher in BT + TTT (89% vs. 67%, p<0.017).
- NS difference: complications, metastasis-free (93% vs. 81%) and overall survival rates (91% vs. 81%), or in visual outcomes.

**Applicable?**
- Tumour regression: SS higher in BT + TTT (63% vs. 49%, p=0.036) vs. BT alone.
- 5-year tumour recurrence rate: SS lower in BT + TTT (96% vs. 83%, p<0.034)
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**Conclusions**
AUTHORS’ CONCLUSIONS: Combined Tx of choroidal melanoma with ruthenium BT and simultaneous TTT seems to provide higher local control, eye-globe preservation, and recurrence-free survival rates than treatment with BT alone and results in similar rates of metastases and overall survival.

**Additional comments on quality of study**
Good; retrospective
Unable to assess all aspects of methodology, so have answered with 'not reported' to many of the questions.

**Grading:** 3
Non-analytic studies (for example, case reports, case series)

<table>
<thead>
<tr>
<th>Study Type</th>
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**Results**
- Tumors were classified as small in 10.5%, medium in 78.4%, and large in 9.2% of pts.

**Applicable?**
- Tumors were classified as small in 10.5%, medium in 78.4%, and large in 9.2% of pts.

**Conclusions**
- Tumors were classified as small in 10.5%, medium in 78.4%, and large in 9.2% of pts.
- 5 and 10-year observed overall survival rates = 83.3% and 71.5%.
- Corresponding relative rates = 95.5% and 94%.
- Factors predicting survival = tumor diameter, patient age, and secondary enucleation.
- N= 106 pts (18%) underwent enucleation up to 14 years after plaque treatment.
- Only predictive factor for enucleation was tumor size.
- At 5 years, 31% pts retained 0.5 visual acuity or better, and 49% retained better than 0.1 visual acuity.
- Predictive factors for visual deterioration were visual acuity and distance from posterior tumor border to the foveola.

AUTHORS’ CONCLUSIONS: After ruthenium brachytherapy for UM, the survival rates and visual outcomes in this population-based investigation were similar to previously published results. The eye was retained in 81.7% of patients. Careful pt selection (presently we only treat melanomas 7 mm or smaller in height) and life-long monitoring for recurrences is warranted.

Additional comments on quality of study
Good


Study Type
Case Series

Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results

Applicable? Conclusions

- Tx: Brachytherapy - 106Ru/106Rh plaques with a notch for the optic nerve. Eye and optic nerve phantoms were fabricated, loaded with small-volume thermoluminescent dosimeters, treated with active plaques, and the radiation dose determined at the optic disc and along the optic nerve. The median dose within the anterior optic nerve was 51.2 Gy (range 10.3-60.5 Gy).
- Population: N=93 juxtapapillary choroidal melanomas
- Follow-up: 10 yrs

RESULTS:
- Choroidal melanoma control (after Tx): N=79 (85%)
- Enucleation: N=14 eyes (15%) due to tumor regrowth.
- 5 and 10 years probability of:
  1. Complete radiation optic neuropathy (RON): 23% and 53%
  2. Developing partial RON: 66% and 82%.
  3. Retaining visual acuity better than 0.5: 38% and 26%.
- No dose-response relationship could be established from the ophthalmological, morphological and functional findings.
- Eyes following plaque irradiation with 50 Gy or more in the center of the optic nerve experienced significant radiation optic neuropathy, other eyes did not.

Additional comments on quality of study
Retrospective; directly applicable population, reasonable sized study, long follow-up
Tumor control, eye preservation, and visual outcomes of ruthenium plaque brachytherapy for choroidal melanoma

Marconi DG, de Castro DG, Reboucas LM, Bernardes Gil GO, Fogaroli RC, Conte Maia MA, Gobo Silva ML, ssis Pellizzon AC, Motono Chojniak MM.

Methods: retrospective analysis
Follow-up: median 39 (6-83) months.
Outcomes: tumor control (local control [LC] and progression-free survival [PFS]) and ocular preservation (enucleation-free survival [EFS]).

RESULTS:
- 2-year LC, PFS, and EFS were 96.2%, 96.2%, and 95.5%.
- 5-year LC, PFS, and EFS were 93.6%, 93.6%, and 84.1%.
- Preinsertion visual acuity (VA) maintenance = 34% (equal or better than pre-Tx).
- Approx. 56% pts stayed with a minimum functional VA of 0.1 or more, from whom more than half stayed with 0.5 or more.
- Cataract: 16% of treated eyes
- Glaucoma: the rarest complication (only 3%)

AUTHORS’ CONCLUSIONS: Small- and medium-sized choroidal melanomas can be adequately treated with (106)Ru brachytherapy, with high rates of tumor control and ocular preservation. Moreover, acceptable incidence of complications such as glaucoma and cataract are seen, and a reasonable part of patients stay with a minimum functional VA.
### Results

**Applicable? Conclusions**

Tx: Ruthenium plaque. EXCLUSIONS: Those who had Ruthenium-106 brachytherapy combined with local resection, prior tumour Tx, adjuvant diode laser or local resection.

**Population:** N= 240 pts with UM. Median tumour thickness = 3.1mm (0-8), median largest basal diameter = 9.1mm (1.5-20.9). Median age = 65 yrs (range:29-94), gender distribution was equal. 14 ciliary body and 226 choroidal melanomas were treated.

**Methods:** retrospective case note review

**Follow-up:** median 47 mths

**RESULTS:**

- Initial response to brachytherapy: 97%.
- Median tumour thickness and largest basal diameter decreased to 1.9mm (0-9.8) and 7.5mm (0-18.7) final follow up.
- Final tumour response rate: 80.3%.
- Additional Tx required: for recurrence/non-response (n=39), or other complications (n=13).
- Complications: (17.5%) included scleral necrosis, neovascular glaucoma or raised IOP, vitreous haemorrhage, non-proliferative radiation retinopathy, macular oedema, optic neuritis and chronic uveitis.
- 5-year predicted eye retention rate: 85.6%.
- Vision of >=6/18 was retained in 58.5%.
- 5-year predicted overall survival and disease-specific survival: 82.7% (95% CI:77.2%, 88.2%) and 92.5% (95% CI:88.4%, 96.6%).
- 50% of tumour recurrence/non response occurred in pts with lesion size >10.9mm, representing 25%of the study population.

**AUTHORS’ CONCLUSIONS:** Ruthenium-106 brachytherapy was associated with high rate of ocular retention, preservation of vision, low tumour-related mortality. A 2mm margin from tumour edge to plaque edge is associated with a lower risk of local tumour relapse

### Additional comments on quality of study

| Conference abstract | Retrospective study; directly applicable population, large study, reasonable follow-up time. |


<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td><strong>Patient Characteristics</strong></td>
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<tr>
<td></td>
<td>Inclusion/Exclusion</td>
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</table>

### Results

**Applicable? Conclusions**

Tx: Ruthenium-106 irradiation brachytherapy.

**Population:** N=213 pts with malignant UM.

**Methods:** Retrospective study.

**Follow-up:** up to 10 years

**RESULTS:**
- Survival (5 and 10 yrs): 82% (SE 2.7%) and 72% (SE 3.4%).
- Local recurrence (5 and 10 yrs): 21.7% (SE 3.0%) and 24.3% (SE 2.8%).
- Enucleation (5 and 10 yrs): 18.0% (SE 2.7%) and 19.2% (SE 2.8%).
- Maculopathy: N=61 (29%), retinal vascular occlusion: N=36 (17%), local recurrence: N=33 (16%), and enucleation: N=38 (18%).
- Age and large tumor diameter = associated with survival (P<.0001 and P<.0075).
- Age <40 and posterior melanoma = significant risk factors for maculopathy (P<0.0085 and P<0.0004) and vascular occlusion (P<0.0415 and P<0.0114).
- Diameter and Bruch membrane rupture = significant predictors (P<0.0032 and P<0.0390, respectively) of local recurrence.
- Visual acuity <20/100:26/97 (27%) cases of anterior but 34/42 (81%) of posterior tumor (P<0.001).

AUTHORS’ CONCLUSION: Although percentage tumor recurrence was high, survival was comparable to series using other treatments. Radiation-related complication rates were acceptable, especially for anterior tumors. Ruthenium therapy can, therefore, be recommended for small and medium-sized tumors with anterior location.

Additional comments on quality of study
Retrospective study; directly applicable population, large study, very long follow-up time.

8742 Eccentric ruthenium plaque radiotherapy of posterior choroidal melanoma 2012
Russo A, Laguardia M, Damato B.

Graefe’s archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie

Study Type: Case Series
Number of patients
Follow-up
Outcomes recorded
Applicable? Conclusions

Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators

Results

Applicable? Conclusions
Tx: eccentric ruthenium(106) (Ru-106) brachytherapy. Plaque positioned eccentrically with its posterior edge aligned with the posterior tumor margin to reduce the radiation dose to the optic disc and fovea.
Population: N=54 pts with choroidal melanoma extending to within 5mm of the optic disc or fovea.
Methods: Unclear from abstract if retro- or pro- spective study
Follow-up: 4 yrs post Tx

RESULTS:
- Tumors had mean longest basal diameter of 12.0mm and mean thickness of 3.1mm. The posterior tumor margin extended to within 3mm of the fovea in 30 patients (56%).
- Visual acuity ≥6/12 at 4 yrs: retained in 74.9% of 24 eyes with posterior tumor margin located 3.1-5.0mm from fovea (95% CI 55.5-94.3%).
- Visual acuity ≥6/12 at 3 yrs: retained in 25.3% of 30 eyes with tumor extension to within 3.0mm of fovea (95% CI, 5.3-45.3%).
- Recurrence at posterior tumor margin: N=2 pts.

AUTHORS’ CONCLUSIONS: Eccentric ruthenium(106) plaque radiotherapy of posterior choroidal melanoma achieves good rates of local tumor control and conservation of vision if special measures are taken to ensure that the plaque is positioned correctly.

Additional comments on quality of study
Unclear from abstract if retro- or pro- spective study; directly applicable population, quite small study, long follow-up time.
Population: N=100 eyes with malignant UM
Tx: irradiated with ruthenium-106 plaques
Follow-up: median 3 years (range 4 months to 10.1 years).

RESULTS:
- Visual Acuity increased for some time in 14 eyes.
- 3 years VA ≥20/70, 20/200, counting fingers, and light perception were retained in 27%, 41%, 67% and 82% of eyes.
- Macular pathology caused loss of reading vision
- Neovascular glaucoma or enucleation caused loss of light perception.
- Multivariate significant risk indicators for:
  1. Loss of VA levels 20/70 and 20/200 = tumor height >5 mm.
  2. Level CF = location of tumor within 1 disc diameter of optic disc, either alone or in addition to the fovea (RR 6.3, 95% CI 4.1-9.8). Also largest basal tumor diameter.
  3. Losing light perception = large TNM size (T3), RR 10.0; 95% CI 4.5-22.5), then proximity of tumor to optic disc (RR 4.3, 95% CI 2.4-7.8).

AUTHORS’ CONCLUSION: Ruthenium brachytherapy may retain vision in an eye with a malignant melanoma of the uvea for a considerable period of time. The data presented are useful in patient counseling and allow comparison to subsequent series.
Tx: irradiation with ruthenium-106 plaques; median apical and scleral dose was 100 Gy (range 15-200) and 1000 Gy (range 200-1200).

Population: N=100 eyes with malignant UM.

Methods: retrospective

Follow-up: median 2.8 and 2.0 yrs (range 1 mth-10 yrs) for anterior & posterior segment complications.

RESULTS (Multivariate):
Strongest risk indicator for:
- radiation cataract (RR 1.5, 95% CI 1.4-1.6) and vitreous haemorrhage (RR 1.6, 95% CI 1.4-1.8) was: height of the tumour
- neovascular glaucoma: TNM class (RR 6.2, 95% CI 2.7-13.8)
- radiation maculopathy: location of posterior tumour margin within 2 mm of fovea (RR 3.4, 95% CI 2.0-6.0)
- radiation optic neuropathy: location of tumour margin within 1 DD of optic disc (RR 6.1, 95% CI 3.0-12.4).

- 3 and 5 year probabilities of avoiding enucleation: 92% and 85%.
- Enucleation: N=10 eyes (due to recurrent tumour growth, Tx complications, or mistakenly suspected extraocular growth).

AUTHORS’ CONCLUSION: The results suggest that the frequency of radiation related complications after ruthenium brachytherapy of uveal melanoma is acceptable, in particular as regard irradiation of small and medium sized tumours for which ruthenium therapy generally is recommended.

Additional comments on quality of study

Retrospective study; directly applicable population, reasonably sized study, long follow-up time.

### Proton beam radiotherapy

**Grading:** 1+

**Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**

**Study Type**

Randomised Controlled Trial

**Number of patients**

151 patients (half on each Tx)

**Study aim/Intervention**

Proton beam radiotherapy with systematic addition of TTT after. For the TTT a diode laser emitting in the red range at a wavelength of 810 nm was used. Irradiation field included a safety margin of 2.5 mm around the tumour. The median characteristics of laser spots for patients treated by TTT were diameter 2 mm, spot intensity 500 mW and duration of each spot 3 min.

**Comparators**

Proton beam radiotherapy (usual technique). Dose: cobalt-60 Gray equivalents delivered in 4 fractions of 15 Gy on 4 days. Seven patients in the proton-beam-radiotherapy-only group received an application of TTT following the development of a complication (particularly massive exudation from the tumour scar or appearance of glaucoma). Nine patients in the proton-beam-radiotherapy-and-TTT group did not receive TTT because of retinal detachment or vitreoushaemorrhage.

**Follow-up**

Median: 38 months.

**Outcomes recorded**

Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients

statistical analysis was performed according to the initial randomization, as it is the rule in randomized studies.

**Results**

No statistically significant difference was observed between the 2 groups in terms of cataracts, maculopathy, papillopathy and glaucoma. In the proton-beam-radiotherapy-only group 41 patients developed glaucoma, and the mean peak intraocular pressure recorded during treatment was 34.5 mm Hg. In the TTT group 35 patients developed glaucoma, and the mean peak intraocular pressure during treatment was 31 mm Hg. These figures are not significantly different, but the analysis of the course of glaucoma in the 2 groups showed that the patients who had received TTT presented less severe glaucoma, with intraocular pressure that tended to return to normal after several months of treatment. A tendency towards a reduction of the number of retinal detachments over time was observed in the TTT group (not significant; p = 0.14). A more marked reduction of tumour thickness was observed in the TTT group (p = 0.06), and the secondary enucleation rate was significantly lower in the TTT group (p = 0.02).

**Applicable?**

The indications and benefits of TTT after proton beam therapy need to be further studied, and the optimal TTT protocol should be defined.

**Conclusions**

Additional comments on quality of study

**Study Type**

Systematic Review

**Number of patients**

Comparative studies only (N=5)

**Results**

- **Tx:** proton beam radiotherapy (PBRT)
- **POPULATION:** UM only.
- **STUDIES:** N=5 comparative studies; large differences in radiation techniques applied within the studies, and variation in pt characteristics within and between studies.

**RESULTS:**

- **Overall:** LOW LEVEL OF EVIDENCE
- **PBRT vs. I-125 or Ru-106 brachytherapy:**
  1. PBRT no beneficial effects on overall survival
  2. PBRT SS > vision preservation (97% vs. 93%, p=0.009)
- **PBRT vs. enucleation:**
  1. PBRT more pts survived (2 studies: 12% more pts over 36 mths and 21% over 60 mths).
- **Complications (PBRT):** 1 study - refractory neovascular glaucoma and corneal perforations, 10.9% eyes enucleated due to complications
- **No economic evaluation studies were found.**
AUTHORS’ CONCLUSIONS: There is limited evidence on the effectiveness and safety of proton radiation in patients with ocular melanomas due to the lack of well-designed and well-reported studies. Available comparative studies suggest that proton beam therapy may be beneficial for patients with uveal melanoma, with, however, possible serious side effects. There is a need for research establishing its cost-effectiveness.

Additional comments on quality of study
Unable to assess all aspects of methodology from abstract

<table>
<thead>
<tr>
<th>Grading:</th>
<th>2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</th>
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</table>

<table>
<thead>
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<td>Patient Characteristics</td>
<td>Inclusion/Exclusion</td>
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<tr>
<td>Study aim/Intervention</td>
<td>To compare iodine 125 (125I) plaque brachytherapy with transscleral tumor resection (TTR) of large uveal melanomas.</td>
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</table>

<table>
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<tr>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>Brachytherapy: Mean: 33 mths / Resection: 24 months.</td>
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</table>

1579 Iodine 125 plaque brachytherapy versus transscleral tumor resection in the treatment of large uveal melanomas
Bechrakis NE, Bornfeld N, Zoller I, Foerster MH, Ophthalmology 2002 Oct

109 1855 1861
The present study suggests that patients with large uveal melanomas who are eligible for transscleral resection have better long-term visual function and lower incidence of radiation-induced complications, such as neovascularization and secondary glaucoma, when compared with patients treated by 125I brachytherapy. This study is outdated because of improvements in surgical technique but still shows that visual outcomes are better after resection than after iodine-125 brachytherapy in patients with a large tumour.

### Additional comments on quality of study

- **Patient Characteristics**
  - **Inclusion/Exclusion**
  - **Study aim/Intervention**
    - Identification of risk factors for subsequent morbidity which, like those for eyelid damage, could be determined at the initial assessment.

- **Comparators**
  - The hospital records from a first cohort of 127 patients treated by protons from 1989 to 1992 were reviewed retrospectively. We gave one point for a tumour too large to be treated by plaque and another point to presence of a retinal detachment visible on indirect ophthalmoscopy. The total score is marked out of 2 and is the sum of these two variables.

- **Follow-up**
  - 36 months

- **Outcomes recorded**
Results

- Of the 127 study patients, 43 (34%) developed rubeosis.
- Seventeen patients (13%) required subsequent enucleation and 16 died (13%) from metastatic disease within the study period.

The two variables that proved to be consistently predictive for the development of rubeosis were LTD (see Fig 1) and the presence of retinal detachment. This scoring system was highly predictive for the subsequent development of rubeosis (log rank test, p < 0.00005) with 35/40 (88%) of cases scoring 2 developing rubeosis by 4 years compared with 19/52 (37%) scoring 1 and 3/35 (9%) scoring 0 (see Fig 3). Fifteen patients underwent enucleation as a result of treatment related morbidity and one underwent enucleation for failure to control the primary tumour (and this case was handled as a censored observation for the subsequent analyses).

Applicable? Yes.

Conclusions

Rubeosis following proton beam radiotherapy depends on the tumour characteristics and that the outcome in terms of morbidity and possibly also of mortality can be predicted by a simple clinical scoring system based on the clinical features at presentation.

The retrospective data collection gives rise to concern.

Additional comments on quality of study

Comparison of clinical outcomes for patients with large choroidal melanoma after primary treatment with enucleation or proton beam radiotherapy

Mosci C, Lanza FB, Barla A, Mosci S, Herault J, Anselmi L, Truini M.

Ophthalmologica Journal international d'ophtalmologie International journal of ophthalmology Zeitschrift fur Augenheilkunde

Study Type Cohort

Number of patients N=132

Patient Characteristics Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up 5 years

Outcomes recorded See below

Results

- NS difference between groups for: cumulative all-cause mortality, melanoma-related mortality and metastasis-free survival (log-rank test, p = 0.56, p = 0.99 and p = 0.25, respectively).
- Eye retention at 5 yrs = 74% (SD 6.2%) in PBRT group .
- Best-corrected visual acuity (BCVA): at Dx = 0.1 or better in 73% of eyes, after 12 and 60 mths, this was 47.5 and 32%.

Applicable? Yes.

Conclusions

AUTHORS’ CONCLUSION: Although enucleation is the most common primary treatment for large uveal melanomas, PBRT is an eye-preserving option that may be considered for some patients

Additional comments on quality of study Retrospective cohort Info from abstract, so unable to assess all aspects of methodology. Have thus put 'not reported' for most of the answers.

Comparison of episcleral plaque and proton beam radiation therapy for the treatment of choroidal melanoma

2083

1999
iodine-125 (125I) episcleral plaque radiation therapy

1. ruthenium-106 (106Ru) episcleral plaque radiation therapy; 2. proton beam radiation therapy (PBRT)

Mean 44.7 months

Tumour recurrence

AUTHORS’ CONCLUSION: Patients treated with 106Ru had a significantly greater risk of local tumor recurrence than did those patients treated with either 125I or PBRT.

- Pts treated with 106Ru had SS > risk of local tumor recurrence vs. 125I (RR 2.97, 95%CI 1.26-7.02; P = 0.0133)
  vs. PBRT (RR 2.94, 95% CI 1.30-6.66; P = 0.0097).
- NS diff between PBRT and 125I groups for tumour recurrence.
- Maximal basal diameter was a significant covariate (P = 0.0033).
- Metaastatic disease: N=7 125I, N=7 106Ru, N=25 PBRT
- Enucleation: N=11 (5.8%) 125I, N=7 (5%) 106Ru and N=29 (10.9%) PBRT.
- Refractory neovascular glaucoma: N=4 125I and N=15 PBRT.

AUTHORS’ CONCLUSION: Patients treated with 106Ru had a significantly greater risk of local tumor recurrence than did those patients treated with either 125I or PBRT.

Additional comments on quality of study

Retrospective

Grading: 3  Non-analytic studies (for example, case reports, case series)

520  Proton beam radiotherapy in the management of uveal melanoma: Clinical experience in Scotland 2009


Study Type  Case Series

Number of patients  Patient Characteristics Inclusion/Exclusion

Study aim/Intervention  Comparators  Follow-up  Outcomes recorded

Results

Applicable? YES

Conclusions

Retrospective study (pts records, data from post-Tx reviews at 3, 6, 12, and 24 months). Mean follow up was 38.8 mths
RESULTS:
- 97% had initial Tx response;
- 87% had successful control of tumor growth (Mean pre-Tx tumor height = 6.2 mm v.s. 4.8 mm post-irradiation, p < 0.001).
- Pre-irradiation VA was <3/60 in 18.5% vs. 74% post-irradiation (p < 0.0001).
- Significant association between AEs (enucleation, metastasis) and greater maximal basal tumor diameter.
- N=18 eyes were enucleated.
- Median survival time estimate = 54 mths.

AUTHORS’ CONCLUSION: In our experience, PBRT is a precise, reliable and effective Tx for management of large, and previously treated UMs. It prevents enucleation in the majority at short term follow-up.

Additional comments on quality of study Good
N=76 pts (reasonable size), retrospective study, directly applicable population (UM), long follow-up


Study Type Case Series
Number of patients 150 patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
To evaluate the long-term local tumour control results and metastasis rate after TSR and to identify possible risk factors.
Comparators
The surgical technique used in this series was similar to the lamellar scleral dissection and choroidectomy under systemic arterial hypotension described by Foulds. After resection a pure SF6 gas bubble (0.5-1.0 ml) was injected in the vitreous cavity and the adjuvant radiotherapy group had a 20.0 mm106Ru plaque (CCB; BEBIG, Berlin, Germany) placed on the excision bed. The prescription point for plaque dosimetry was defined in all cases as the apex of an imaginary 5.0-mm thick tumour receiving 100 Gy. The mean scleral dose was 470 Gy, ranging between 400 and 500 Gy.
Follow-up Median: 37 months.
Outcomes recorded

386 Ten-year results of transscleral resection of large uveal melanomas: local tumour control and metastatic rate
2010

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

A residual tumour was diagnosed in nine cases. The residual tumours were treated with TTT (n=3), argon laser photocoagulation (in the pre-TTTera) (n=2) or 106Ru plaque brachytherapy (n=3), and one eye was enucleated. Three of the eight salvaged eyes later developed tumour recurrence.

Tumour recurrences were detected in 26 eyes, between 4 and 78 months after TSR: 18 intraocular (unifocal/multifocal), six episcleral and two orbital. Predictive factors for recurrent tumour were: lack of 106Ru brachytherapy (p=0.001; HR 4.5),
Further improvement of tumour control may be achieved by using a larger 106Ru plaque or possibly by implementing preoperative beam radiotherapy with a homogeneous tumour dose distribution (eg, proton beam teletherapy), sparing susceptible eye structures such as the optic disc and macula. Whether this strategy will reduce ocular morbidity and, even more importantly, have an impact on patient survival remains to be elucidated by further studies.

Applicable? Conclusions

Preoperative retinal detachment (p=0.046; HR 7.8), LBD (p=0.035; HR 2.4) and age =>50 years (p=0.046; HR 2.6)

Additional comments on quality of study

8997  Clinical and histopathologic findings after photodynamic therapy of choroidal melanoma  2012

Canal FJ, Salomao DR, Robertson D, Cantrill HL, Koozekanani D, Rath PP, Pulido JS, Retina

Study Type  Case Series

Number of patients

Patient Characteristics  Study aim/Intervention  Comparators  Follow-up  Outcomes recorded

Results

Applicable? Conclusions

Tx: Photodynamic therapy (PDT)

POPULATION: N=5 pts with pigmented choroidal melanoma (CM)

METHODS: clinical and histopathologic features of CM after PDT.

Follow-up: approx 1 week post-Tx surgery

RESULTS:

- N=3 pts had PDT + intravitreal bevacizumab 1 wk pre-biopsy and brachytherapy to minimize the risks of bleeding during the biopsy
- N=2 pts had primary Tx with PDT for peripapillary amelanotic melanomas (N=1 + bevacizumab).
- Tumors treated with PDT + bevacizumab:
  1. Marked reduction in tumor vascularity (indocyanine angiography)
  2. Biopsies were conducted without recognizable bleeding, showing viable tumor cells.
- Tumors receiving PDT as a primary Tx:
  1. Were followed by progressive tumor growth that led to enucleation years after.
  2. Histopathology revealed overlying fibrosis with invasion of sclera and optic nerve.

AUTHORS' CONCLUSION: Photodynamic therapy and bevacizumab can induce closure of the superficial vasculature of a pigmented choroidal melanoma, but in none of our cases, there was evidence of tumor destruction from this treatment. Preoperative PDT may be useful to reduce the potential of bleeding at the time of tumor biopsy. Our cases do not support the use of a single session of PDT as a primary treatment for pigmented small choroidal melanomas

Additional comments on quality of study

Directly applicable population; Follow-up = short but applicable to study (as looking at histopath features post-Tx); very small study;
Population: N=886 UM; TNM stages of malignant tumours: n=39 T1 (4%), n=420 T2 (47%), n=409 T3 (46%), n=18 T4 (2%); means: age = 63 years, tumour thickness = 5.7mm, diameter = 15.7mm.

Rx: proton beam radiotherapy

Retrospective study

Median follow-up: 63.7 months

RESULTS:
- overall survival rate at 5 years: 92% for T1, 89% for T2, 67% for T3, and 62% for T4
- overall survival rate at 10 yrs: 86% for T1, 78% for T2, 43% for T3, and 41% for T4.
- Factors associated with increased death rate: advanced age, tumor thickness, largest tumor basal diameter, tumor volume, and tumor volume-to-eyeball volume ratio.
- Metastasis-free survival rates: 88.3 % at 5 years and 76.4 % at 10 years.
- Local control: 4.96% of pts
- Local control rates: 93.9% at 5 years and 92.1% at 10 years.
- Ocular conservation rates: 91.1% at 5 years and 87.3% at 10 years.

AUTHORS’ CONCLUSIONS: Large series of patients treated for UM with a very long follow-up. Despite the large tumor volume treated, our results were similar to previously published findings relating to proton beam therapy.
- Tx: Medicyc Cyclotron 65 MeV proton beam; 52 Gy (57.20 Gy Co-equivalent dose) on 4 days.
- Population: N=538 pts with UM; Tumours: n=349 posterior pole (64.9%), n=130 equatorial (24.1%), and n=59 ciliary body (11%). N=204 pts (37.9%) had T1 or T2, N=334 pts (62.1%) had T3 or T4 tumors. Median tumor diameter = 14.6 mm, and median height = 5.1 mm.
- Follow-up: 78 months

RESULTS at 78 months:
- CSS = 77.4%
- Overall survival = 73.8%
- Local control = 89.0%
- CSS was not influenced by patient age or site of the tumor (81.5% for T1 and T2 vs. 75% for T3 and T4; P = 0.035).
- Most important parameter affecting outcome: tumor diameter, rather than the height
- Metastatic rate = 8% and depended on T stage, tumor diameter, thickness, but not site.
- Enucleation: N=38 (most due to tumor progression and/or glaucoma).

1/3 of pts with adequately scored visual acuity pre- and post-Tx had a stable, if not improved vision, and half the patients retained useful vision post-Tx. CONCLUSION:
The outcome of patients suffering from uveal melanoma and treated with high-energy protons compares favorably with other techniques of treatment. The tumor dimensions affected CSS and metastatic rate. Even though two-thirds of patients had posterior pole tumors, half of them retained useful vision.

Additional comments on quality of study
Unclear if prospective (seems to be)

Seems to be prospective; directly applicable population; large study, long follow-up

Endoresection of choroidal melanoma
1998
Damato B, Groenewald C, McGalliard J, Wong D.
British Journal of Ophthalmology
213 218

Study Type: Case Series
Number of patients: Primary endoresection: 41 patients.

Patient Characteristics
Inclusion/Exclusion
The results of 52 endoresections for choroidal melanoma are reported

Comparators
The tumour and surrounding normal choroid are removed piecemeal with the vitreector, leaving an area of bare sclera. Next, fluid-air exchange is performed so that all subretinal fluid drains into the choroidal coloboma, from where it is aspirated with a flute needle. After several minutes, once the retina has flattened, a double row of confluent endolaser burns is applied around the coloboma to create retinal adhesion. In addition, the entire bed of the coloboma and the margins of the choroid are treated with strong laser burns, to destroy any residual tumour cells. The eye is filled with silicone oil, which is removed after approximately 12 weeks.

Follow-up: Median: 20 months

Outcomes recorded
Cryotherapy is applied to the sclerotomies to destroy any tumour cells that may have seeded to these areas. If the tumour has indistinct margins or extends far peripherally, a 15 mm or 20 mm ruthenium plaque is sutured to the sclera to cover as much of the coloboma as possible, without extending less than 1–2 mm from the optic nerve. The plaque is removed after a dose of approximately 100 Gy has been delivered to a depth of 3 mm.

Endoresection of uveal melanoma may conserve the eye and vision when other forms of conservative treatment are likely to cause severe ocular complications. The main problem following endoresection is retinal detachment which, unlike radiational optic neuropathy, is preventable and usually treatable. Further studies are required to establish the efficacy of endoresection with regard to local tumour control and metastatic disease.

Additional comments on quality of study

Study Type: Case Series

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

To report on outcomes after proton beam radiotherapy of choroidal melanoma using a 62-MeV cyclotron in patients considered unsuitable for other forms of conservative therapy

Comparators

The simulation procedures included: (1) evaluation of several candidate gaze directions, from which the optimum was selected, that is, the one giving minimal radiation to optic nerve, lens, fovea, and lacrimal gland; (2) measurement of any ocular torsion, when the eye was in the selected treatment position; (3) detection of

Follow-up

Of the 336 patients treated more than 1 year before analysis, follow-up information exceeding 1 year was

Outcomes recorded

Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience

Damato B, Kacperek A, Chopra M, Campbell IR, Errington RD.

International Journal of Radiation Oncology, Biology, Physics

1127

2005

62 1405 1411
any visual limitations that might have prevented steady gaze during treatment, in which case a more suitable gaze direction was selected; and (4) assessment as to whether to retract the eyelid or treat through the closed lid, in which case eyelid thickness, shape, and position were measured. Adjunctive transpupillary thermotherapy at the time of the proton beam radiotherapy was given in 11 patients to prevent exudation (5 patients) to reduce symptomatic exudative retinal detachment (2 patients) and to reduce the radiation safety margin (4 patients). A further 23 patients received TTT as a treatment for exudation from the irradiated tumor. One patient received photodynamic therapy as a secondary treatment for macular edema. Six patients had transscleral local resection of the irradiated tumor as treatment for the exudative retinal detachment. Two patients had transretinal enucleation of the tumor for exudation. Minimum visual conservation time of 20/40 or better was measured from the time of treatment to the last date when this level of vision was documented. A similar protocol was followed for measuring visual conservation time of 20/200 or better and counting fingers or better.

Results

The cumulative risk of local treatment failure at 5 years was 3.5% (95% confidence interval [CI], 1.21–5.83%). Cox univariate analysis showed the only significant predictive factors to be longest basal tumor dimension (p = 0.01; risk ratio, 1.24/mm; 95% CI, 1.05–1.47) and increased tumor height (p = 0.014; risk ratio, 1.31/mm; 95% CI, 1.06–1.63). The actuarial rate of enucleation was 1.6% (95% CI, 0.2–3.0%) at 1 year, 4.0% (95% CI, 1.6–6.1%) at 2 years, and 9.4% (95% CI, 5.4–13.5%) at 5 years. Cox univariate analysis found the factors associated with increased risk of enucleation to be ciliary body involvement (p = 0.0001, risk ratio 2.57; 95% CI, 1.56–4.21); posterior tumor extension (p = 0.045; risk ratio, 0.67; 95% CI, 0.43–1.00); longest basal dimension (p = 0.0001; risk ratio, 1.30 per mm; 95% CI, 1.15–1.47); tumor height (p = 0.0001; risk ratio, 1.55 per mm; 95% CI, 1.34–1.80); and retinal invasion (p = 0.024; risk ratio, 4.07; 95% CI, 1.20–13.79). The reasons for enucleation were neovascular glaucoma (9 patients) and local tumor recurrence (8 patients), with other reasons being retinal fibrosis (1 patient), retinal detachment (3 patients), bullous keratopathy (1 patient), and patient choice (1 patient). Vision of 6/12 or better was present in 212 patients before treatment and was conserved in 63.5% (95% CI, 55.9–71.1%) at 2 years, 44.8% (95% CI, 35.3–54.4%) at 5 years, and 32.2% (95% CI, 21.1–43.2%) at 8 years.
Proton beam radiotherapy achieves high rates of ocular conservation and local tumor control in patients considered unsuitable for other forms of conservative treatment. There is appreciable ocular morbidity, however, which correlates strongly with tumor size. This sample is biased by the fact that patients with a large ocular tumour tended to be treated by local resection or enucleation. Many patients lost vision despite the fact that the optic disc and fovea did not receive any radiation and this is because of exudation from the irradiated tumour ('toxic tumour syndrome').

**Applicable? Conclusions**

Cox univariate analysis showed that the variables predicting loss of 20/40 vision were: reduced initial visual acuity (p = 0.007; risk ratio, 1.37 per Snellen line; 95% CI, 1.09–1.71) and posterior tumor extension (p = 0.001; risk ratio, 1.58; 95% CI, 1.22–2.05). Visual acuity of 20/200 or better was present in 301 patients before treatment and conserved in 81.9% (95% CI, 77.2–86.6%) at 2 years, 61.1% (95% CI, 54.1–68.1%) at 5 years, and 41.7% (95% CI, 32.4–51.0%) at 8 years.

Cox univariate analysis showed that the variables predicting loss of visual acuity of 20/200 or better were: reduced initial visual acuity (p = 0.002; risk ratio, 1.15 per Snellen line; 95% CI, 1.05–1.26), tumor height (p = 0.001; risk ratio, 1.16/mm; 95% CI, 1.06–1.27), and retinal invasion (p = 0.0001; risk ratio, 5.00; 95% CI, 2.11–11.7).

**Additional comments on quality of study**

**1124** Proton beam radiotherapy of iris melanoma 2005

**Study Type** Case Series

**Number of patients**

- **Patient Characteristics**
  - Inclusion/Exclusion

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

- **Applicable?**
- **Conclusions**

Populaton: N=88 pts with iris melanoma (mean age 52 yrs)

Tx: proton beam radiotherapy, with 53.1 Gy in 4 fractions.

Median follow-up: 2.7 yrs

**RESULTS:**

- Tumors had median diameter of 4.3 mm, involving more than 2 clock hours of iris in 32% of patients and more than 2 hours of angle in 27%.
- Ciliary body was involved in 20%.
- Cataract: N=13 patients before Tx and subsequently developed in another 18.
- Cataract had a 4-year rate of 63% and was related to age (p < 0.05), initial visual loss (p < 0.0001), iris involvement (p < 0.0001), and tumor thickness (p < 0.0001).
- Glaucoma: N=13 pts before Tx and developed after treatment in another 3.
- N=3 eyes were enucleated (due to recurrence), which had an actuarial 4-year rate of 3.3% (95% CI 0-8.0%).

**AUTHORS' CONCLUSIONS:** Proton beam radiotherapy of iris melanoma is well tolerated, the main problems being radiation-cataract, which was treatable, and preexisting glaucoma, which in several patients was difficult to control

**Additional comments on quality of study**

Fair

Reasonable follow-up, directly applicable population, reasonable sample size.
This study reports the results of proton beam radiotherapy based on a retrospective series of patients treated for uveal melanoma at the Orsay Center. A total dose of 60 cobalt Gray equivalent (CGE) was delivered in 4 fractions on 4 days. Survival rates were determined using Kaplan–Meier estimates. Prognostic factors were determined by multivariate analysis using the Cox model.

73 months. Thirty-one patients (2.2%) were lost to follow-up (25 patients with no evidence of disease and 6 patients with metastatic disease at last follow-up).

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Proton beam radiotherapy for uveal melanoma: results of Curie Institut-Orsay proton therapy center (ICPO) 2006

Study Type

Case Series

Number of patients

1406 patients

Inclusion/Exclusion

This study reports the results of proton beam radiotherapy based on a retrospective series of patients treated for uveal melanoma at the Orsay Center.

A total dose of 60 cobalt Gray equivalent (CGE) was delivered in 4 fractions on 4 days. Survival rates were determined using Kaplan–Meier estimates. Prognostic factors were determined by multivariate analysis using the Cox model.

73 months. Thirty-one patients (2.2%) were lost to follow-up (25 patients with no evidence of disease and 6 patients with metastatic disease at last follow-up).

The 5-year local control rate was 96% (range, 95.4–96.6%). Two independent unfavorable prognostic factors were identified on multivariate analysis: large tumor diameter (>13 mm) with a relative risk (RR) of 2.18 (95% CI, 1.21–3.91; p = 0.003) and small macular area (<41%) receiving >=30 CGE with RR of 2 (95% CI, 1.12–3.57; p = 0.01).

Enucleation performed for local recurrence was excluded from this analysis. Ninety-nine patients (7%) underwent enucleation for complications: neovascular glaucoma with severe pain in 83 patients, loss of vision in 5 patients, and for an unknown cause in 1 patient. Two independent unfavorable prognostic factors were identified on multivariate analysis: large tumor thickness (>4.8 mm) with RR 5.42 (95% CI, 2.87–40.23; p = 0.001) and large lens volume (>43%) receiving >=30 CGE with RR 2.47 (95% CI, 1.48–4.12; p = 0.0002).

At 5 years, visual acuity remained stable for 38% of patients, decreased for 56% of patients, and improved for 6% of patients. Actuarial 5-year complication rates were: Maculopathy 66.5% (95% CI, 63.3–69.7); Papillopathy 23.4 (95% CI, 20.5–26.3); Glaucoma 28.6% (95% CI, 26–31.2); Cataract 61.8% (95% CI, 59–64.7); Keratitis 11.5% (95% CI, 9.6–13.4); Vitreous hemorrhage 13.9% (95% CI, 11.9–16); and Intraocular inflammation 27.5% (95% CI, 24.9–30.1).

Applicable? Conclusions

BERTIL's INFO: This retrospective study confirms that proton beam radiotherapy ensures an excellent local control rate. Further clinical studies are required to decrease the incidence of postirradiation ocular complications. This is not really a retrospective study but a prospective study because results are reported according to baseline variables and not outcomes.

It is not stated whether the data were collected prospectively or retrospectively. IT SAYS RETROSPECTIVE

Population: N=1,406 UM pts (excluded pts with previous local Tx, metastases, extrascleral tumor invasion, or iris melanoma at Dx. Tumors: 4.4% anterior, 41.8% at the equator, 53.8% posterior. Extensive retinal detachment=26.4%, unknown=0.3%. Means: diameter=13.3mm, thickness=5.4mm.
Tx: Proton beam radiotherapy. Total dose of 60 CGE was delivered in 4 fractions on 4 days.

METHODS: Retrospective study

Median follow-up was 73 months (range, 24-142 months)

RESULTS:
- 5-year overall survival and metastasis-free survival rates: 79% and 80.6%
- 5-year local control rate: 96%.
- 5-year enucleation for complications rate: 7.7%.
- Prognostic factors for overall survival: age (p < 0.0001), gender (p < 0.0003), tumor site (p < 0.0001), tumor thickness (p = 0.02), tumor diameter (p < 0.0001), and retinal area receiving at least 30 CGE (p = 0.003).
- Prognostic factors for metastasis-free survival: age (p = 0.0042), retinal detachment (p = 0.01), tumor site (p < 0.0001), tumor volume (p < 0.0001), local recurrence (p < 0.0001), and retinal area receiving at least 30 CGE (p = 0.002).
- Prognostic factors for local control: tumor diameter (p = 0.003) and macular area receiving at least 30 CGE (p = 0.01).
- Prognostic factors for enucleation for complications: tumor thickness (p < 0.0001) and lens volume receiving at least 30 CGE (p = 0.002).

AUTHORS’ CONCLUSION: This retrospective study confirms that proton beam radiotherapy ensures an excellent local control rate. Further clinical studies are required to decrease the incidence of postirradiation ocular complications.

Additional comments on quality of study
- Good: Huge study, directly applicable population, long follow-up, retrospective

Study Type
- Case Series

Number of patients
- 2435 melanomas in 2432 patients

Patient Characteristics
- Inclusion/Exclusion
- Patients with documented tumor regrowth following PBRT, and identify the probable risk factors for these recurrences. We also describe the changes to the treatment procedure to improve the rate of local tumor control.

Comparators
- Three to seven tantalum clips (diameter 2.5 mm, thickness 0.5 mm) were sutured onto the outer surface of the sclera to mark the border of the tumor base, as perceived from its shadow during transillumination. Treatment was planned using the EYEPLAN program developed originally by Goitein and Miller. Shape of the aperture corresponding to the tumor shape in treatment position surrounded by a safety margin of usually 2 mm. Treatment was delivered in 4 fractions, usually on 4 consecutive days. Most of the patients were treated with a proton dose of 54.5 Gy, which corresponds to 60 CGE (Co-60-Gy equivalent)

Follow-up
- 40 months

Outcomes recorded
- Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma
- 2001

The actuarial rate of local tumor control for the entire group of patients was 95.8 ± 0.5% at 5 years and 94.8 ± 0.7% at 10 years (Kaplan–Meier estimate).

In 29/51 cases, the growing tumor was localized in the distal part of the target volume, in 22/51 cases, in the ciliary body.

Eleven of 73 tumors showed continued growth within the original target volume.

Four of 73 recurrences grew totally outside the target volume.

Nine recurrences (26.5%) occurred among 34 eyes treated with reduced safety margin, vs. 64 recurrences (2.7%) among 2,401 eyes treated with standard or increased safety margin. In the entire group of 73 recurrences, 22 appeared in the ciliary body, of which 14 were identified to be ring melanomas.

Since 1989, we knew that an eyelid within the irradiation field could be the cause of local tumor regrowth in the distal part of the target volume due to an inadequate estimation of eyelid thickness, leading to a reduced range not covering the whole target volume.

Risk factors for local tumor control failure were identified as a reduction of the safety margin, large tumors infiltrating the ciliary body, the presence of an eyelid within the irradiation field, inadequate delimitation of the tumor border by tantalum clips, and male gender. Measures to maximize local control rates were: using standard safety margins in all cases, increasing the safety margin for large ciliary body tumors, introducing a new eyelid model in the treatment planning software, and delimiting all sides of the tumor by clips.

Since 1989, we knew that an eyelid within the irradiation field could be the cause of local tumor regrowth in the distal part of the target volume due to an inadequate estimation of eyelid thickness, leading to a reduced range not covering the whole target volume.

Applicable? Yes

Conclusions

Additional comments on quality of study

1465 Eye retention after proton beam radiotherapy for uveal melanoma. 2003


Study Type Case Series

Number of patients

Patient Characteristics Inclusion/Exclusion

Study aim/Intervention Comparators

Follow-up Outcomes recorded

Results

Applicable? Yes

Conclusions

Population: N=2645 pts (2648 eyes) with UM; Age range 9-90yrs, N=1284 men. Largest tumor diameter ranged from 4 to 27.5 mm, and tumor height from 0.9 to 15.6 mm.

Tx: proton beam radiotherapy.

Follow-up: median 44 months.

RESULTS:
- Overall eye retention rate post-Tx: 5 yrs = 88.9%; 10 yrs = 86.2%; 15 yrs = 83.7%
- Enucleation: N=218 eyes (related to larger tumor size, mainly tumor height, proximity of posterior tumor margin to optic disc, male gender, high intraocular pressure, and large degree of retinal detachment at treatment time).
- After optimization of Tx technique, eye retention rate at 5 yrs increased from 97.1% to 100% for small tumors, from 86.7% to 99.7% for medium, and from 71.1% to 89.5% for large tumors.

AUTHORS' CONCLUSIONS: The Tx technique as used today results in excellent eye retention rates, even in less favorable cases such as large tumors and tumors located close to the optic disc. The experience and a continuous quality control program allowed us to improve the 5-year eye retention rate for all tumor sizes. These findings demonstrate the positive impact of experience and quality control-based efforts for treatment technique optimization.

Additional comments on quality of study

PROSPECTIVE, directly applicable population, very large study, long follow-up

2274 Predictive factors for the development of rubeosis following proton beam radiotherapy for uveal melanoma
British Journal of Ophthalmology 81 748 754

Study Type
Case Series

Number of patients
Patient Characteristics
Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable? Yes

Conclusions

Tx: Proton beam radiotherapy
Population: N=127 pts with primary UM
Methods: Retrospective review of hospital records.
Outcomes: Presence of rubeosis = measure of significant ocular damage.

RESULTS:
- Risk factors for developing rubeosis: Large tumor size and presence of retinal detachment
- Predictors of subsequent enucleation for uncontrolled ocular pain: same factors as above.
- Pts with tumors too large to plaque and with associated retinal detachment had a 90% chance of developing rubeosis within 4 years of proton beam radiotherapy.

AUTHORS' CONCLUSIONS: Pts with a UM too large for plaque therapy and an associated retinal detachment run a very high risk of developing rubeosis after proton beam radiotherapy and one third of individuals developing rubeosis required enucleation for pain even if local tumor control was satisfactory

Additional comments on quality of study

retrospective

Retrospective study; directly applicable population; reasonable sample size; long follow-up

712 Endoresection in high posterior choroidal melanomas: long-term outcome
British Journal of Ophthalmology 92 1040 1045
The results of primary and salvage endoresection are presented. The safety and efficacy of the procedure are assessed. The surgical technique varied depending on the degree of retinal involvement. If the tumour had not invaded the retina, 20-gauge vitrectomy was followed by posterior hyaloid dissection, 120u anterior retinotomy, and 810 nm diode laser endophotocoagulation (800–100 mW) 2 mm beyond the tumour margins. Melanoma was removed with the vitrectomy probe. Cellular remnants at the scleral bed were photocoagulated with high doses (800–1000 mW) of endodiode laser. The retina was reattached with liquid perfluorocarbon and air. Laser retinopexy endophotocoagulation was performed at the limits of the retinotomy and was followed by fluid–air exchange and silicone oil–air exchange. If the tumour had invaded the retina, the diode laser was applied through the retina, and the tumour and retina were removed together. Silicone oil was removed at 3 months. Since January 2003, adjunctive brachytherapy treatment has been performed following surgery in primary cases to prevent local recurrence, with the exception of one patient (case 33) who refused radiotherapy. A ruthenium 106 plaque was sutured to the sclera to cover as much of the coloboma as possible. The plaque was removed after a dose of approximately 80 Gy had been delivered to a depth of 3 mm.

Results At the latest visit, 35/38 (92.1%) patients still retained the eye. Final visual acuity was as follows: less than 20/400 in 27 patients, from 20/400 to 20/100 in eight patients, and better than 20/100 in three patients. The main postoperative complication was retinal detachment after silicone oil removal, which was done in 36 patients; among them, 10 had retinal detachment (26% of the series). Other postoperative complications included bleeding at the scleral bed (100%), early postoperative ocular hypertension in 12 patients (31.5%), epiretinal proliferation in four (11%), postradiation retinopathy in two, severe subretinal fibrosis in one,
In large uveal melanomas it may preserve the eye and vision, whereas other forms of conservative treatment are likely to cause severe ocular complications, with enucleation the only alternative treatment. Long-term follow-up of these patients did not show a higher risk of metastasis or local recurrence, and survival rates were similar to other techniques, although comparisons are difficult because of the unusual presentation of this type of melanoma.

Applicable? Yes

Conclusions

Additional comments on quality of study

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>2069 patients.</td>
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<table>
<thead>
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<th>Inclusion/Exclusion</th>
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<tbody>
<tr>
<td>Study aim/Intervention</td>
<td>To determine outcomes after proton beam radiotherapy.</td>
</tr>
<tr>
<td>Comparators</td>
<td>50-100 Cobalt grey equivalents in five fractions over 7-10 days.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Median follow-up in surviving patients was 9.4 years</td>
</tr>
<tr>
<td>Outcomes recorded</td>
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</tbody>
</table>

Results

Tumor regrowth occurred in 60 patients, and 95% of tumors (95% confidence interval, 93%-96%) were controlled locally at 15 years. Risk scores were developed for the other 3 outcomes studied. Overall, the treated eye was retained by 84% of patients (95% confidence interval, 80%-87%) at 15 years. The probabilities for vision loss (visual acuity worse than 20/200) ranged from 100% to 20% at 10 years and for death from tumor metastases from 95% to 35% at 15 years, depending on the risk group. Risk factors for enucleation were tumour thickness, proximity to disc and fovea, tumour diameter, tumour pigmentation and tumour shape. Risk factors for visual loss were proximity to optic disc and fovea, tumour thickness, Visual acuity at baseline, retinal detachment, diabetes and basal tumour diameter.

Applicable? Yes

Conclusions

Evidence-based estimates of outcome in patients irradiated for intraocular melanoma

Gragoudas E. Li W. Goitein M. Lane AM. Munzenrider JE. Egan KM. Archives of Ophthalmology 2002

N=2069 pts with intraocular melanoma (unilateral or ciliary body, without evidence of systemic metastasis)

Tx: proton beam radiation; 70 CGE in 5 fractions over 7-10 days in 95% pts (others = slightly higher or lower doses).

Follow-up: median in surviving patients = 9.4 years

RESULTS:

- Tumor regrowth: N=60 pts
- Local control at 15 yrs: 95% of tumors (95% CI, 93%-96%)
- Treated eye retention at 15 yrs: 84% pts (95% CI, 80%-87%)
- Probability of vision loss (visual acuity worse than 20/200): range 100% - 20% at 10 yrs
- Probability of death from tumor metastases: range 95%-35% at 15 years, depending on risk group.

CONCLUSIONS: High-dose radiation treatment was highly effective in achieving local control of intraocular melanomas. In most cases, the eye was salvaged, and
functional vision was retained in many patients. The mortality rate was high in an identifiable subset of patients who may benefit from adjuvant therapies directed at microscopic liver metastases.

Additional comments on quality of study
Good

RETROSPECTIVE, directly applicable population, huge study, long follow-up

1785  Intraocular inflammation after proton beam irradiation for uveal melanoma 2001

Study Type  Case Series
Number of patients  Population: N=?? (says 'large series'); pts with UM; 28% of these had ocular inflammation
Study aim/Intervention  Follow-up  Outcomes recorded

Results

Applicable? Yes
Conclusions
Population: N=?? (says 'large series'); pts with UM; 28% of these had ocular inflammation
Follow-up: median 62 mths

RESULTS:
- Risk factors were mainly tumour related and were correlated with: larger lesions (height > 5 mm, diameter > 12 mm, volume > 0.4 cm(3)).
- Multivariate analysis: 2 most important risk factors = initial tumour height and irradiation of a large volume of the eye.
- Ocular inflammation usually consisted of mild anterior uveitis, resolving rapidly after topical steroids and cycloplegics.
- Incidence of inflammation after proton beam irradiation of melanomas seems higher than previously reported and is related to larger lesions.
- Evidence of inflammation associated with UM seems to be associated with tumour necrosis (spontaneous or after irradiation).
- The appearance of transient inflammation during follow-up may be related to the release of inflammatory cytokines during tumour necrosis.

AUTHORS’ CONCLUSION: Inflammation following proton beam irradiation is not unusual. It is correlated with larger initial tumours and may be related to tumour necrosis.

Additional comments on quality of study
Retrospective; directly applicable population, unknown size of study - just says 'large series', long follow-up

1045  Proton beam therapy for iris melanomas 2006

Study Type  Case Series
Number of patients  Study aim/Intervention  Comparators  Follow-up  Outcomes recorded
- **Tx**: proton beam irradiation (60 Gy delivered in four fractions to the tumour volume).
- **Population**: iris melanomas (Excluded ciliary body melanomas with iris involvement or tumours with extrascleral invasion). N=5 pts had lesion with documented growth. Median clinical diameter = 5mm (2-8), median ultrasound diameter = 4.8mm (2-7.7). Tumour grades: 6% T1, 57.1% T2, and 14.3% T3 all N0M0. 71.4% had iridocorneal angle invaded by tumour.
- **Methods**: Retrospective review of pts charts
- **Follow-up**: median 33 months (8-72).

**RESULTS:**
- N=100% alive with no proven metastatic disease (N=1 pt suspicious liver lesions).
- N=0 tumour progression or ocular relapse.
- Tumour response at 2 years: flat lesion (6.3%), partial regression (75%), stable (18.8%).
- N=0 required secondary enucleation.
- Main complications: cataract (45% within 24 months of Tx).
- 15% had raised intraocular pressure, but no neovascular glaucoma.

**AUTHORS’ CONCLUSIONS:** Proton beam therapy shows potential utility for selected cases of localised iris melanomas allowing excellent local tumour control and eye preservation. Further follow-up on larger series is needed to confirm these results.

**Additional comments on quality of study**
- Retrospective, small study
- Retrospective, directly applicable population, small study, long follow-up

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**Applicable?**
- Yes

**Conclusions**
- Proton beam therapy for the treatment of uveal melanoma in Scotland

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**Study Type**
- Case Series

**Number of patients**
- Patient Characteristics
  - Inclusion/Exclusion

**Study aim/Intervention**
- Comparators
- Follow-up
- Outcomes recorded

---

**Results**

**Applicable?**
- Yes

**Conclusions**
- Tx: treated initially with PBT
- Population: N=147 ciliary body or choroidal melanoma, mean age 62.3 yrs, 94.6% choroidal melanomas. 97.8% of all treated melanomas were of medium or large size
- Methods: data from retrospective review of case notes, database information, PBT planning data, ultrasound and pathology reports.

**RESULTS:**
- Enucleation 22.4% (mean time to this = 23.8 mths), main reasons were suspected recurrence (48%) and neovascular glaucoma (42%).
- Metastatic death: 9.5% (the mean time to this = 28.9 months).
- 5-year eye retention rate: 71.3%.
- Disease-specific survival rate: 87.7%.
AUTHORS' CONCLUSION: PBT is reserved for the Tx of mainly medium-sized and large-sized uveal melanomas in Scotland. The eye retention and disease-specific survival rates confirm its suitability as an eye-preserving primary treatment in these patients. It is evident that PBT is a conservative treatment option for uveal melanoma, including those of larger size.

Additional comments on quality of study
Retrospective; directly applicable population, reasonable sized study, reasonable follow-up time.

8873 Proton beam therapy for iris melanoma: Review for 78 cases
8873 Proton beam therapy for iris melanoma: Review for 78 cases 2012
Mammar H, Herault J, Angelier G, Grange JD, Caujolle JP, Mosci C, Chauvel P. Radiotherapy and Oncology Conference 102

Study Type Case Series
Results

Applicable? Yes
Conclusions

Tx: proton beam therapy (52 Gray in four fractions and four days to the tumour volume)
Population: N=75 iris melanoma, 43 females, mean age = 56 years (range 19-92). TNM staging system: 52 T1 (66%), 14 T2 (18%), 12 T3 (15%).
Methods: retrospective study
follow-up: median 50 mths (mean 60.5, range 15-136).

RESULTS:
- N=1 tumour progression and treated by the second proton beam.
- N=1 secondary enucleation.
- 51% developed cataract
- N=3 presented aggravation of a pre-existing glaucoma.
- N=3 (4%) died of a cause unrelated to the iris melanoma
- N=2 (2.5%) lost to follow up.

AUTHORS' CONCLUSIONS: Proton beam therapy appears to be an alternative of choice for the conservative treatment of iris melanomas with an excellent tumoral control for acceptable complications.

Additional comments on quality of study
Retrospective; directly applicable population, reasonable sized study, long follow-up time.

1793 Choroidal melanoma treatment with proton beam: First nine years of experience of the genoa ocular oncology group
1793 Choroidal melanoma treatment with proton beam: First nine years of experience of the genoa ocular oncology group 2001

Study Type Case Series
Results

Applicable? Yes
Conclusions
Results

Applicable? Conclusions
Tx: Proton beam therapy
Population: N=127 pts, OM
Follow-up: 9 years (average 21 +/- 5 mths with some pts up tol 72 months).

RESULTS:
- Local tumour control: 96.8% of cases
- Eye retention: 93.8%.
- Visual acuity > 2/10: 30% (T1/T2 tumours) and 21% (T3 tumours)
- Death due to metastasis: N=7 pts
- Global survival rate after 42 mths: 90%

Additional comments on quality of study
Prospective study; directly applicable population, reasonable sized study, long follow-up time.

2437  Visual-field deficits associated with proton beam irradiation for parapapillary choroidal melanoma. [Erratum appears in Ophthalmology 1996 May;103(5):699]
Park SS, Walsh SM, Gragoudas ES.

Study Type
Case Series

Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results

Applicable? Conclusions
Tx: proton irradiation
Population: N=59, parapapillary choroidal melanoma
Methods: Retrospective review of pts
Follow-up: at least 18 mths post-Tx

RESULTS:
- 19 pts (31%) = Dx of radiation papillopathy.
- Progressive visual-field loss**: 67% pts with radiation papillopathy and 73% without papillopathy.
- In both groups, visual-field loss correlated with the area of the retina predicted to be exposed to irradiation in the majority of patients.

** absolute scotoma > [corrected] or equal to 30 degrees as compared with the pre-Tx visual field.

AUTHORS’ CONCLUSIONS: Progressive visual-field loss is common after proton irradiation for parapapillary choroidal melanoma. However, the scotoma usually correlates with the area of the retina exposed to irradiation. The development of radiation papillopathy does not appear to be associated with additional visual-field defects in most cases.
Proton beam therapy for iris melanoma: a review of 15 cases

Rundle P, Singh AD, Rennie I.

Retrospective study; directly applicable population, fair sized study, reasonable follow-up time.

- Tx: proton beam therapy
- Population: N=15 pts with nonresectable iris melanomas; 11/15 had ocumented growth (inc. n=2 local recurrence following iridocyclectomy); N=3 were biopsy-proven melanoma. N=1 had newly acquired vascular nodule of the iris associated with angle seeding and glaucoma.
- Methods: retrospective
- Follow-up: mean 34 month

RESULTS:
- Tumour control (34 mths): 93% (14/15 eyes).
- Common complications included: glaucoma in 53% (n=5 had glaucoma pre-Tx), dry eye (27%) and cataract in three patients (20%).
- Eye retention: 80% (n=12).

AUTHORS’ CONCLUSION: Proton beam therapy is an effective treatment for cases of nonresectable iris melanoma. The major complications are cataract and glaucoma.

Resection

Grading: 2+

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
INTERVENTION: Iodine brachytherapy in Finland or TSR in United Kingdom

MAIN OUTCOMES: Tumor control, complications, and visual acuity. Time to event (hazard ratio, HR) data (prospectively collected, adjusted for matching)

AUTHORS' CONCLUSIONS: This study suggests that TSR preserves 20/200 vision better than IBT and avoids some of its major complications, but increases the risk of local recurrence. About 350 patients would need to be randomized to prove that TRS preserves 20/60 vision better than IBT.

Results - Risk of local recurrence: smaller after IBT vs. after TSR (HR = 0.02, 95% CI 0.01-0.11, P<0.001)
- All-cause and melanoma-specific survivals (8 yrs): NS difference (HR = 0.81, 95% CI 0.30-2.22, P=0.69).
- Risks of cataract (HR = 2.05, 95% CI 1.08-3.89, P = 0.029), maculopathy (HR = 2.28, 95% CI 0.96-5.43, P=0.062), and vitreous hemorrhage (HR = 2.30, 95% CI 0.95-5.57, P=0.064) were higher after IBT.
- Rubeosis, neovascular glaucoma, and optic neuropathy developed only after IBT.
- Risk of retinal detachment, exudative after IBT and rhegmatogenous after TSR (HR = 0.84, 95% CI 0.40-1.75, P=0.63), and risk of losing 20/60 vision (HR = 1.37, 95% CI 0.76-2.45, P=0.29) were comparable between the groups.
- Risk of losing 20/200 vision: Higher after IBT (HR = 2.38, 95% CI 1.48-3.83, P<0.001).
- QoL: no overall difference.

Number of patients N=98 (49 pairs of patients)

Study Type Cohort

Patient Characteristics Inclusion/Exclusion

Study aim/Intervention INTERVENTION: Iodine brachytherapy in Finland or TSR in United Kingdom

Comparators transscleral resection (TSR) IN UK vs.iodine brachytherapy (IBT) in FINLAND

Follow-up Unclear from abstract. Some data is given for 8 years

Outcomes recorded MAIN OUTCOMES: Tumor control, complications, and visual acuity. Time to event (hazard ratio, HR) data (prospectively collected, adjusted for matching)

Results - Risk of local recurrence: smaller after IBT vs. after TSR (HR = 0.02, 95% CI 0.01-0.11, P<0.001)
- All-cause and melanoma-specific survivals (8 yrs): NS difference (HR = 0.81, 95% CI 0.30-2.22, P=0.69).
- Risks of cataract (HR = 2.05, 95% CI 1.08-3.89, P = 0.029), maculopathy (HR = 2.28, 95% CI 0.96-5.43, P=0.062), and vitreous hemorrhage (HR = 2.30, 95% CI 0.95-5.57, P=0.064) were higher after IBT.
- Rubeosis, neovascular glaucoma, and optic neuropathy developed only after IBT.
- Risk of retinal detachment, exudative after IBT and rhegmatogenous after TSR (HR = 0.84, 95% CI 0.40-1.75, P=0.63), and risk of losing 20/60 vision (HR = 1.37, 95% CI 0.76-2.45, P=0.29) were comparable between the groups.
- Risk of losing 20/200 vision: Higher after IBT (HR = 2.38, 95% CI 1.48-3.83, P<0.001).
- QoL: no overall difference.

Applicable? Yes

Conclusions

AUTHORS' CONCLUSIONS: This study suggests that TSR preserves 20/200 vision better than IBT and avoids some of its major complications, but increases the risk of local recurrence. About 350 patients would need to be randomized to prove that TRS preserves 20/60 vision better than IBT.

Additional comments on quality of study Prospective COHORT INFO IS FROM ABSTRACT ONLY SO UNABLE TO GET FULL METHODOLOGICAL DETAILS - SO WRITEEN 'NOT REPORTED' FOR SOME ANSWERS

Grading: 3 Non-analytic studies (for example, case reports, case series)

1753 Vitreoretinal surgery and endoresection in high posterior choroidal melanomas Garcia AJ, Sararols L, Martinez V, Corcostegui B, Retina 2001

Number of patients N=98 (49 pairs of patients)

Study Type Case Series

Patient Characteristics Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up Unclear from abstract. Some data is given for 8 years

Outcomes recorded MAIN OUTCOMES: Tumor control, complications, and visual acuity. Time to event (hazard ratio, HR) data (prospectively collected, adjusted for matching)

Results - Tx: internal resection of the tumor;
1. If retina not invaded by tumor, vitrectomy performed followed by posterior hyaloid dissection, 120 degrees anterior retinotomy, endophotocoagulation 2 mm past tumor margin, melanoma removal with vitreotomy probe, retinal reattachment with liquid perfluorocarbon and air, and silicone oil exchange.
2. If tumor invaded retina, laser was applied through retina, and retina + tumor removed together.

Applicable? Yes

Conclusions

AUTHORS' CONCLUSIONS: This study suggests that TSR preserves 20/200 vision better than IBT and avoids some of its major complications, but increases the risk of local recurrence. About 350 patients would need to be randomized to prove that TRS preserves 20/60 vision better than IBT.

Additional comments on quality of study Prospective COHORT INFO IS FROM ABSTRACT ONLY SO UNABLE TO GET FULL METHODOLOGICAL DETAILS - SO WRITEEN 'NOT REPORTED' FOR SOME ANSWERS

Grading: 3 Non-analytic studies (for example, case reports, case series)

1753 Vitreoretinal surgery and endoresection in high posterior choroidal melanomas Garcia AJ, Sararols L, Martinez V, Corcostegui B, Retina 2001
Population: N=25 high posterior choroidal melanomas >9 mm thickness, diameter <15mm; mean age 46.6 yrs. Tumor thicknesses: 9.1-12.8 mm, tumor diameter: 8.9-14.8 mm. Mean pre-op visual acuity was 20/60. N=11 pts tumor had invaded retina.

Methods: Prospective, consecutive pts.
Follow-up: range 12 to 72 months.

RESULTS:
- Entire tumour removed: all N=25 eyes.
- Main post-op complications: cataract (40%), retinal detachment (16%), macular traction (16%), and epiretinal macular proliferation (8%).
- Mean post-op visual acuity: 20/100.
- No tumors recurred, and there was no evidence of metastasis.

AUTHORS’ CONCLUSIONS: These data suggest that internal resection of high posterior melanomas may conserve ocular and functional vision and does not seem to increase the risk of metastatic disease. Longer follow-up is necessary to establish the safety of the procedure.

Additional comments on quality of study
Prospective? Prospective?, directly applicable population, small sample size, reasonable to long follow-up.

Stereotactic Radiosurgery
Grading: 1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

<table>
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<tr>
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<th>Metaanalysis</th>
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<td>Study aim/Intervention</td>
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<td>Comparators</td>
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<td>Follow-up</td>
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<td>Outcomes recorded</td>
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</table>

8928 Charged particle radiation therapy for uveal melanoma: A systematic review and meta-analysis 2013

Results

Applicable? Conclusions

Additional comments on quality of study
Good quality; recent search until Jan 2012

- Efficacy and AEs of CPT for UM.
- Clinical trials and observational studies of CPT (protons, helium ions, and carbon ions).
- N=27 studies enrolling 8809 UM pts included.
- Rate of local recurrence = SS less with CPT than brachytherapy (OR 0.22, 95% CI 0.21-0.23).
- NS diffs in mortality or enucleation rates (although CPT had 47% lower risk of enucleation).
- CPT = lower retinopathy and cataract formation rates.

AUTHORS’ CONCLUSIONS: data suggest better outcomes may be possible with charged particle therapy with respect to local recurrence, retinopathy, and cataract formation rates. The overall quality of the evidence is low, and higher quality comparative effectiveness studies are needed to
Survival and complications following γ knife radiosurgery or enucleation for ocular melanoma: a 20-year experience.


Study Type: Cohort

Results:
- The 5-year survival rates were: 64% for 35 Gy, 62.71% for 45 Gy, 63.6% for 50-70 Gy and 65.2% for enucleated patients.
- Complications: using 35 Gy led to more than a 50% decrease, when compared with the 45-Gy dose, in the incidence of cataract, glaucoma and retinal detachment. Retinopathy, optic neuropathy and vitreous haemorrhage were not significantly influenced.
- Blindness decreased dramatically from 83.7% for 45 Gy to 31.4% for 35 Gy (p = 0.006), as well as post-radiosurgery enucleation: 23.9% for 45 Gy vs 6.45% for 35 Gy (p = 0.018). Visual acuity, recorded up to 5 years post-radiosurgery, was significantly better preserved for 35 Gy than for 45 Gy (p = 0.0003).

Conclusions:
- To present experience in treating ocular melanoma at the National Centre for Stereotactic Radiosurgery in Sheffield, UK over the last 20 years. Non-randomised.
- Using 35 Gy led to a dramatic decrease in complications, vision loss and salvage enucleation, while not compromising patient survival.

Additional comments on quality of study

Survival and complications following Gamma Knife radiosurgery or enucleation for ocular melanoma: A 20-year experience

Dinca EB, Yianni J, Rowe J, Radatz MWR, Preotiu-Pietro D, Rundle P, Rennie I, Kemeny AA

Acta Neurochirurgica 154(4): 605-610
Gamma Knife radiosurgery: Different peripheral doses (using the 50% therapeutic isodose) were employed: 50-70 Gy for 24 patients, 45 Gy for 71 patients, 35 Gy for 62 patients.

**AUTHORS' CONCLUSIONS:** Using 35 Gy led to a dramatic decrease in complications, vision loss and salvage enucleation, while not compromising patient survival.

### Study Type
- **Number of patients**
  - N=790: N=170 (gamma Knife) + N=620 (enucleation)

### Results
- **Survival:** NS diff between 35-Gy, 45-Gy and 50- to 70-Gy groups and with the enucleation group
- **5-year survival:** 64% (35 Gy); 62.7% (45 Gy), 63.6% (50-70 Gy) and 65.2% (enucleation).
- **Clinical variables influencing survival for radiosurgery pts:**
  1. Tumour volume (SS)
  2. Tumour location (median 66 vs 37 mths for juxtapapillary vs peripheral tumours) (SS)
  3. NS = age and gender.
- **Complications:**
  1. Incidence of cataract, glaucoma and retinal detachment: 35 Gy >50% decrease vs.45-Gy
  2. Retinopathy, optic neuropathy and vitreous haemorrhage: NS influenced.
  3. Blindness: SS decrease from 83.7% for 45 Gy to 31.4% for 35 Gy
  4. Post-radiosurgery enucleation: SS decrease 23.9% for 45 Gy vs 6.45% for 35 Gy.
- **Visual acuity (up to 5 years post-radiosurgery):** SS better preserved for 35 Gy vs. 45 Gy.

### Additional comments on quality of study
- UK study; retrospective
- Unable to assess all methodological aspects from abstract, so have answered 'not reported' to many of the questions.

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Retrospective evaluation of patients with uveal melanoma treated by stereotactic radiosurgery with and without tumor resection

Suesskind D, Scheiderbauer J, Buchgeister M, Partsch M, Budach W, Bartz-Schmidt KU, Ritz R, Grisanti S, Paulsen F.

### Study Type
- **Number of patients**
  - N=78 (N=60 SDRT, N=18 combination).

### Results
- **Recurrences:** N=6 and N=0 (SDRT vs. combi)
- **Local control at 3 years:** 86% vs.100% in group 2 (P=0.22, NS).
- **Eye preservation rate at 3 yrs:** 77% vs 87% (P=0.82, NS).
AUTHORS' CONCLUSIONS AND RELEVANCE Survival analysis suggested that SDRT with combined tumor resection might be associated with increased tumor control and fewer radiation complications than SDRT as monotherapy. Both groups had similar eye retention rates and were comparable concerning the decrease in visual function in most eyes. However, the protocol was stopped after 3 unexplained deaths after surgery.

- Visual acuity decrease: median loss -18 Snellen lines vs. -22 Snellen lines
- SDRT had more (NS): retinopathies (P=0.07), opticopathies (P=0.27), rubeotic glaucomas (P=0.10)
- NS difference in development of metastases (P=0.33).
- Overall survival: NS difference (N=2 unexplained deaths post-surgery in COMBI grp (P=0.06).

Applicable? Yes

Conclusions

- Visual acuity decrease: median loss -18 Snellen lines vs. -22 Snellen lines
- SDRT had more (NS): retinopathies (P=0.07), opticopathies (P=0.27), rubeotic glaucomas (P=0.10)
- NS difference in development of metastases (P=0.33).
- Overall survival: NS difference (N=2 unexplained deaths post-surgery in COMBI grp (P=0.06).

Additional comments on quality of study

Grading: 2- Case-control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tr>
<td>Cohort</td>
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<td>Metastasis free survival</td>
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</table>

Results

- Only variables that influenced survival rates were tumour location (p = 0.002), ciliary body tumours with the worst prognosis, and tumour volume. The 5-year cumulative metastasis-free survival rate was 51% in the enucleation treatment group compared to 74% in the stereotactic treatment group.
- In multivariate analysis there was no statistical difference in survival rates between the two treatment groups.

Applicable? Conclusions

- A non-randomized, retrospective study to determine whether metastasis-free survival following stereotactic radiosurgery is comparable with that following enucleation in a cohort of patients with choroidal and ciliary body melanoma.
- Tumour size and location at presentation determined metastasis-free survival. Large ciliary body tumours had the highest risk of metastasis. Metastasis-free survival after stereotactic radiosurgery was comparable to that after enucleation.

Additional comments on quality of study
To evaluate long-term local tumor control, visual acuity, and survival after hypofractionated linear accelerator-based stereotactic photon radiotherapy in patients with choroidal melanoma

Twenty-four patients received a total dose of 70 Gy (five fractions of 14 Gy), 158 a total dose of 60 Gy (five fractions of 12 Gy) and 30 patients a total dose of 50 Gy (five fractions of 10 Gy)

Results

Median tumor height and volume decreased from 4.8 mm and 270.7 mm³ at baseline to 2.6 mm and 86.6 mm³ at the last individual follow-up, respectively (p<0.001, p<0.001)

Local tumor control was 95.9% after 5 years and 92.6% after 10 years

Thirty-two patients developed metastatic disease, and 22 of these patients died during the follow-up period.

Vision: Median visual acuity decreased from 0.55 at baseline to hand motion at the last individual follow-up (p<0.001)

Conclusions

Hypofractionated stereotactic photon radiotherapy with 70 to 50 Gy delivered in five fractions in 7 days is sufficient to achieve excellent local tumor control in patients with malignant melanoma of the choroid

Long follow up but a larger dose given hence good disease control but ? More visual loss

Additional comments on quality of study

Grading: 3 Non-analytic studies (for example, case reports, case series)
Report our experience with linear accelerator-based stereotactic fractionated radiotherapy in the treatment of juxtapapillary choroidal melanoma. 60 Gy (in 10 fractions) for 29 months local control, enucleation-free survival, and complication rates.

### Results
- Four cases of local progression (8%) and three enucleations (6%)
- Actuarial complication rates at 2 and 5 years were 33% and 88%, respectively, for radiation-induced retinopathy; 9.3% and 46.9%, respectively, for dry eye; 12% and 53%, respectively, for cataract; 30% and 90%, respectively, for optic neuropathy; and 18% and 38%, respectively, for neovascular glaucoma.
- Vision: Actuarial visual loss [Snellen acuity (decimal equivalent), <0.1]; 11% and 54% at 2 and 5 years.

### Conclusions
- Linear accelerator-based stereotactic fractionated radiotherapy using 60 Gy in 10 fractions is safe and has an acceptable toxicity profile. It has been shown to be an effective noninvasive treatment for juxtapapillary choroidal melanomas.
- Good result in juxtapapillary tumours.
RESULTS:
- Local progression: N=4 (8%)
- Enucleations: N=3 (6%).
- Local control rates (2 and 5 years): 93% and 86%
- Enucleation-free survival rates (2 and 5 years): 94% and 84%
- Complication rates (2 and 5 years):
  1. 33% and 88% for radiation-induced retinopathy
  2. 9.3% and 46.9% for dry eye
  3. 12% and 53% for cataract
  4. 30% and 90% for visual loss [Snellen acuity<0.1]
  5. 11% and 54% for optic neuropathy
  6. 18% and 38% for neovascular glaucoma.

AUTHORS’ CONCLUSIONS: Linear accelerator-based stereotactic fractionated radiotherapy using 60Gy in 10 fractions is safe and has an acceptable toxicity profile. It has been shown to be an effective noninvasive treatment for juxtapapillary choroidal melanomas.

Additional comments on quality of study
- Retrospective; smallish sample size; SACHIN COMMENT: Good
- Retrospective; directly applicable population; smallish sample size; long follow-up.

2247 Treatment of primary intraocular cancers: retinoblastoma and uveal malignant melanoma 1997 Jul

Study Type Case Series
Number of patients 14
Patient Characteristics Initial results of stereotactic in UK - Dose 70 Gy
Study aim/Intervention
Inclusion/Exclusion
Comparators
Follow-up
Outcomes recorded

Results Regression of the tumour has been observed in 13 patients, whilst the lesion has remained unchanged in one patient.

Significant radiation induced adverse reactions were noted in 13 patients and include; retinopathy, optic neuropathy, rubeosis iridis, and secondary glaucoma. Two patients have required enucleation because of intractable rubeotic glaucoma. One patient has died from proven metastases.

Vision: The visual acuity has deteriorated in all 14 patients.

Conclusions Although stereotactic radiosurgery appears to be a practical and effective method of treating uveal melanomas, its usefulness is limited by a high incidence of radiation induced adverse reactions. Further work is required to refine the current treatment protocol and establish an optimal prescription dose.

Initial results with high dose of radiation

Additional comments on quality of study

8818 Long term side effects after hypofractionated stereotactic photon radiotherapy of choroidal melanoma in 212 patients treated at the General Hospital Vienna (1997-2007) 2012
Population: N=212 pts with choroidal melanoma unsuitable for ruthenium-106 brachytherapy or local resection. n=189 (89.2%) and n=168 (79.2%) of the tumors were within 3 mm of the macula and the optic disc, respectively.

Tx: stereotactically at a Linac with 6-MV photon beams in five fractions with 10, 12, or 14 Gy per fraction.

Follow-up: PROSPECTIVE - every 3 mths in the first 2 yrs, then every 6 mths until 5 years and then once a year thereafter until 10 years after RT.

RESULTS:
- 5 most common AEs: retinopathy and optic neuropathy (n=114 and 107), cataract development (n=87), neovascular glaucoma (n=46), and corneal epithelium defects n=(41).
- Pts free of any radiation retinopathy (33.6%), optic neuropathy (38.5%), cataract (51.2%), neovascular glaucoma (75.5%), or corneal epithelium (77.6%) defects 5 years after RT.

AUTHORS' CONCLUSION: In centrally located choroidal melanoma hypofractionated stereotactic photon radiotherapy shows a low to moderate rate of adverse long-term side effects comparable with those after proton beam radiotherapy. Future fractionation schemes should seek to further reduce adverse side effects rate while maintaining excellent local tumor control.

Additional comments on quality of study
Good - prospective

PROSPECTIVE, directly applicable population, large study, long follow-up
RESULTS:
- Median tumor height and volume decreased from 4.8 mm and 270.7 mm to 2.6 mm and 86.6 mm at last follow-up (p < 0.001, p < 0.001).
- Median visual acuity decrease: from 0.55 to hand motion at last follow-up (p < 0.001).
- Local tumor control was 95.9% after 5 years and 92.6% after 10 years.
- N=32 pts developed metastatic disease
- N=22 pts died during follow-up.

CONCLUSION: Hypofractionated stereotactic photon radiotherapy with 70 to 50 Gy delivered in five fractions in 7 days is sufficient to achieve excellent local tumor control in patients with malignant melanoma of the choroid. Disease outcome and vision are comparable to those achieved with proton beam radiotherapy. Decreasing the total dose below 60 Gy seems to be possible

Additional comments on quality of study

Prospective; directly applicable population; very long follow-up, large study.

7585
Radiogenic side effects after hypofractionated stereotactic photon radiotherapy of choroidal melanoma in 212 patients treated between 1997 and 2007


International journal of radiation oncology, biology, physics

Study Type
Case Series

Number of patients
Patient Characteristics
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Applicable? Yes
Conclusions
Tx: hypofractionated stereotactic photon radiotherapy (using Linac with 6-MV photon beams in five fractions with 10, 12, or 14 Gy per fraction)
Population: N=212 pts with choroidal melanoma unsuitable for ruthenium-106 brachytherapy or local resection
Follow-up: Every 3 mths (first 2 yrs), then every 6 mths until 5 yrs, then once /yr until 10 yrs after Tx

RESULTS:
- N=189 (89.2%) and N=168 (79.2%) of tumors were within 3 mm of the macula and optic disc.
- 5 most common radiotherapy AEs were: retinopathy and optic neuropathy (114 cases and 107 cases, respectively), cataract development (87 cases), neovascular glaucoma (46 cases), and corneal epithelium defects (41 cases).
- In total, 33.6%, 38.5%, 51.2%, 75.5%, and 77.6% pts were free of any radiation retinopathy, optic neuropathy, cataract, neovascular glaucoma, or corneal epithelium defects 5 yrs post-Tx.

AUTHORS' CONCLUSION: In centrally located choroidal melanoma hypofractionated stereotactic photon radiotherapy shows a low to moderate rate of adverse long-term side effects comparable with those after proton beam radiotherapy. Future fractionation schemes should seek to further reduce adverse side effects rate while maintaining excellent local tumor control

Additional comments on quality of study
Good

PROSPECTIVE, directly applicable population, large study, long follow-up

580 Stereotactic radiotherapy for treatment of juxtapapillary choroidal melanoma: 3-year follow-up 2009 Sep
RESULTS (Post-Tx actuarial rates at 37 mths):
- Local tumour control 94%
- Metastases: 15%
- Survival: 90%
- Radiation-induced complications: neovascular glaucoma 42%, cataract 53%, retinopathy 81% and optic neuropathy 64%.
- Secondary enucleation: N=10 pts (16%) - n=4 for tumour recurrence, n=6 for painful neovascular glaucoma.

AUTHORS' CONCLUSIONS: Stereotactic radiotherapy offers a non-invasive alternative to enucleation and brachytherapy in the management of juxtapapillary choroidal melanoma with a high tumour control rate, however, at the expense of a significant rate of long-term ocular complications.
Prospective case series

GKR can be considered an alternative to enucleation for the treatment of choroidal melanomas.

Enucleation sparing procedure

Additional comments on quality of study

Fractionated stereotactic radiotherapy for uveal melanoma, late clinical results

Muller K, Naus N, Nowak PJCM, Schmitz PIM, de PC, van Santen CA, Marijnissen JP, Paridaens DA, Levendag PC, Luyten GPM.

Study Type  | Case Series
--- | ---
Number of patients | 102
Patient Characteristics & Inclusion/Exclusion | Local tumor control= 96%
Study aim/Intervention | 15 enucleation because neovascular glaucoma (NVG) (9), local disease progression (4).
Comparators | 19 developed severe retinopathy,
 | 13 developed optic neuropathy,
 | 10 developed cataract and 10 patients suffered from keratitis sicca.
Follow-up | 32 months
Outcomes recorded | The 5-year actuarial MFS was 75% (95% CIs: 62-84%).

Vision: Best corrected visual acuity (BCVA) decreased from a mean of 0.26 at diagnosis to 0.16, 3 months after radiation and it gradually declined to 0.03, 4 years after therapy.

Applicable? | Yes
Conclusions | To determine local control, late toxicity and metastatic free survival (MFS) of patients treated with fractionated stereotactic radiation therapy (FSRT) for uveal melanoma (UM).

Additional comments on quality of study

To determine local control, late toxicity and metastatic free survival (MFS) of patients treated with fractionated stereotactic radiation therapy (FSRT) for uveal melanoma (UM).

Large series
Short follow up
15% enucleation rate
The use of single fraction Leksell stereotactic radiosurgery in the treatment of uveal melanoma


**Results**

**Applicable?**

---

**Conclusions**

The use of single fraction Leksell stereotactic radiosurgery in the treatment of uveal melanoma

POPULATION: N=14 pts with posterior UM

**RESULTS:**

- Regression of tumour: N=13 pts
- Unchanged lesion: N=1 pts.
- Visual acuity deterioration: N=14 pts.
- Significant radiation induced AEs: N=13 pts (includes retinopathy, optic neuropathy, rubeosis iridis, and secondary glaucoma).
- Enucleation: N=2 pts (due to intractable rubeotic glaucoma).
- Death from proven metastases: N=1 pts.

AUTHORS’ CONCLUSIONS: Although stereotactic radiosurgery appears to be a practical and effective method of treating uveal melanomas, its usefulness is limited by a high incidence of radiation induced adverse reactions. Further work is required to refine the current treatment protocol and establish an optimal prescription dose.

Additional comments on quality of study

Very small study; Unclear if retrospective or prospective; follow-up time unclear (from abstract)
- Tx: plaque radiotherapy. Notched design (126 eyes, 89%), round design (14 eyes, 10%), with iodine 125 (132 eyes, 94%) and cobalt 60 (9 eyes, 6%). Median radiation dose to tumor apex = 8500 cGy. Adjuvant transpupillary thermotherapy used in 54 eyes (39%).
- Population: N=141 pts with juxtapapillary choroidal melanoma overhanging the optic disc. Median age = 61 yrs. Presenting symptoms included reduced visual acuity (72 eyes, 51%), photopsia (14, 10%), and visual field defect (18, 13%); 35 pts (25%) = asymptomatic. Median tumor basal diameter = 11 mm. median thickness = 5.2 mm. Tumor overhung ≤50% of the disc in 88 eyes (62%) and >50% in 53 eyes (38%). In N=19 (13%) tumor overhung entire disc.
- Methods: retrospective medical record review.
- Follow-up: mean of 56 mths

RESULTS:
- Complications included: nonproliferative retinopathy (51%), proliferative retinopathy (22%), maculopathy (37%), papillopathy (48%), neovascular glaucoma (19%), and vitreous hemorrhage (40%).
- Final visual acuity of 20/200 or worse: 72 eyes (77%).
- Visual loss >5 Snellen lines: 59 eyes (63%).
- Enucleation: 27 eyes (23%).
- Tumor recurrence: 12 eyes (10%).
- Metastasis: 15 pts (13%)
- Death: N=4 (3%).

AUTHORS’ CONCLUSIONS: Using plaque radiotherapy for choroidal melanoma overhanging the optic disc, local tumor control was achieved in 90% of cases. Tumor and radiation effects led to poor visual acuity in 77% of eyes. The metastatic rate was 13% and the mortality rate was 3%.

Retrospective study; directly applicable population, reasonably sized study, long follow-up time.
Long-term result of carbon-ion radiation therapy for locally advanced or unfavorably located choroidal melanoma: CT based 2-port orthogonal therapy can reduce the incidence of neovascular glaucoma


Study Type: Case Series

Number of patients

Applicable? Conclusions

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

- Tx: carbon ion radiation therapy (C-ion RT) with CT based treatment planning: phase I/II dose-escalation protocol (n=16 pts 60 GyE, n=78 70 GyE, n=13 77 GyE, and n=7 85 GyE, in 5 fractions). Since Oct 2005, two-port orthogonal therapy started (to reduce of NVG) and done in n=51 pts. Dose-volume histogram analysis additionally done in N=106 pts with regard to NVG occurrence.

- POPULATION: N=114 pts with locally advanced or unfavorably located choroidal melanoma (N=106 T3 and N=8 T2 - UICC 5th edition).

- METHODS: Prospective

- FOLLOW-UP: >6 mnths (median 4.6 years, 0.5-10.6)

RESULTS:

- 5-year overall survival (OS) = 80.4%
- Cause-specific survival (CSS) = 82.2%
- Local control rate = 92.8%
- Distant metastasis free survival rate (DMFSR) = 72.1%
- Eye retention rate = 92.8%,
- neovascular glaucoma (NVG): N=36 pts
- Enucleation: N=3 pts (due to severe glaucoma).
- 3 and 5-year NVG incidence rate: 29.7% and 35.9%

UNIVARIATE: NVG incidence rate of 2-port group was SS lower vs. 1-port group (p< 0.001); 3-year NVG incidence rate = 41.6% and 13.9% for 1-port and two-port group.

MULTIVARIATE: SS risk factors for NVG = tumor size, distance from optic disc (0-3mm vs others), and 1-port therapy

MULTIVARIATE: SS risk factors of OS, CSS, and DMFSR: distance from optic disc (0 vs others).

- Dose-volume histogram analysis: average irradiated volumes of iris ciliary body = SS lower in non-NVG group at all dose levels vs. NVG group.

AUTHORS’ CONCLUSIONS: Long-term result of C-ion RT for choroidal melanoma at our institute was satisfactory, even with tumors of unfavorable size or site. This study suggests tumor size, distance from optic disc, and number of port are related to NVG occurrence; distance from optic disc is related to survival and distant metastasis. CT based two-port C-ion RT can be useful to reduce irradiated volumes of iris ciliary body and resulting risk of NVG

Additional comments on quality of study

Prospective. BERTIL COMMENT: OT available in UK but good data and interesting.

Prospective, good sample size, directly applicable population, long follow-up.
To evaluate prospectively local tumor control and morbidity after fractionated CyberKnife radiosurgery for uveal melanoma unsuitable for ruthenium-106 brachytherapy or local resection.

Prospective case series
CyberKnife fractionated radiosurgery seems to be a viable alternative local treatment modality in uveal melanoma with no serious acute side effects. Further follow-up is indicated.

Small series and follow up. Useful in patients with large posterior juxtapapillary tumours and those with serous detachment?

**Patient Characteristics**

**Study aim/Intervention**

To evaluate prospectively local tumor control and morbidity after fractionated CyberKnife radiosurgery for uveal melanoma unsuitable for ruthenium-106 brachytherapy or local resection.

**Comparators**

8 months local tumor control and morbidity

**Follow-up**

Outcomes recorded

decrease in tumor thickness in three patients and reattachment of the retina in four
Vision: Vision improved minimally in two eyes and remained stable in three

**Study Type**

Case Series

**Number of patients**

5

**Inclusion/Exclusion**

Prospective case series
CyberKnife fractionated radiosurgery seems to be a viable alternative local treatment modality in uveal melanoma with no serious acute side effects. Further follow-up is indicated.
Small series and follow up. Useful in patients with large posterior juxtapapillary tumours and those with serous detachment?

**Applicable?**

Conclusions

**Study Type**

Randomised Controlled Trial

**Number of patients**

N= 60 posterior pole choroidal melanoma

**Inclusion/Exclusion**

N=30 adjuvant ICG before TTT (TTT + ICG)

**Study aim/Intervention**

De PP, Jamart J, Ophthalmology

**Comparators**

N=30 TTT alone (control group); infrared radiation delivered from the diode laser

**Follow-up**

median follow-up: 30 months (range, 6-49 months)

**Outcomes recorded**

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1458 Adjuvant indocyanine green in transpupillary thermotherapy for choroidal melanoma

De PP, Jamart J, Ophthalmology

Grading: 1+

**Results**

decrease in tumor thickness in three patients and reattachment of the retina in four
Vision: Vision improved minimally in two eyes and remained stable in three
Mean initial tumor basal diameter: TTT=7.7 mm, TTT+ICG = 7.38 mm
- Mean initial tumor thickness: TTT = 2.9 mm, TTT+ICG = 3.1 mm
- Mean post-Tx tumor thickness (6 mths): TTT = 1.9 mm (30% reduction), TTT+ICG = 2.2 mm (31% reduction)
- There were 12 tumors (40%) in the TTT group and 15 (50%) in the TTT + ICG group that measured 1.5 mm in thickness, with a flat ophthalmoscopic appearance. Tumor control was achieved in 55 tumors (92%).
- Tumor recurrence: N=2 (TTT) and N=3 (TTT + ICG)
- Predictors of final tumor thickness of 1.5 mm: smaller initial tumor thickness, more TTT sessions, and a tumor location other than temporal.
- No apparent effect of ICG administration before TTT on the final tumor thickness and temporal tumor thickness regression.

AUTHORS' CONCLUSIONS: Despite the efficacy of TTT in the management of selected choroidal melanomas, adjuvant ICG administration before each TTT session does not seem to be beneficial in their regression pattern. Further research in vivo with a larger sample of patients and longer follow-up will be necessary to determine the role of ICG in TTT for choroidal melanomas.

Additional comments on quality of study

INFO IS FROM AN ABSTRACT ONLY SO UNABLE TO ASSES ALL THE METHODOLOGICAL ASPECTS FOR QUALITY (so have written 'not reported'.

Grading: 2+  
Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

8820  The effect of supplemental transpupillary thermal therapy on visual outcomes in choroidal melanoma  2012
Drury B, Chidgey A, Finnigan S, Glasson W.  Clinical and Experimental Ophthalmology  Conference 40

Study Type  Cohort
Number of patients
Patient Characteristics  Study aim/Intervention  Comparators  Follow-up  Outcomes recorded
N=54 TTT group (group A), N=57 non-TTT group (group B).  Indications for supplementary TTT  Mean follow up was 65.3 and 60.1 months for group A and B respectively

Results
1. Indications for supplementary TTT: radiotherapy related complications and signs of early tumour recurrence
2. Poorer levels of visual acuity were found in group A vs. group B (SS effect at 1 and 4 years follow up)
3. Visual acuity immediately following primary brachytherapy: amount of visual acuity loss was equal between group A and B

Applicable?  YES

AUTHORS' CONCLUSIONS: When TTT was used for the treatment of radiotherapy related complications or signs of early tumour recurrence, there was a trend towards poorer visual outcomes but this difference only reached significance at 1 and 4 years during follow up. Accounting for early radiotherapy related vision loss, the addition of TTT did not result in significantly worse visual acuity

Additional comments on quality of study
**Grading: 3 Non-analytic studies (for example, case reports, case series)**

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**Results**

**Tx:** Diode laser transpupillary thermotherapy (TTT) using diode laser OcuLight SLx.

**Population:** N=55 pts (N=57 eyes) with intraocular tumor; age 31-82 yrs (mean 55 yrs).

**Follow-up:** range 2 - 25 mths.

**RESULTS:**
- N=5 pts (5 eyes) were enucleated (inefficient Tx)
- Tumour regression: N=41 (72%) of 57 eyes
- Tumour stabilisation: 7 eyes (12%) and stated progression n=9 (16%).
- Complications and AE: visual field scotomas in treated area, hemorrhage to the vitreous, PVR, secondary neovascular glaucoma and exudative retinal detachment were found during Tx and follow-up.
- EM (electron mic) was better than LM (light mic) and revealed additional zone D which was invisible on LM. No scleral alterations induced by heat were found.

**AUTHORS’ CONCLUSIONS:**
1. In selected cases, TTT can be effective especially in regard to small tumors.
2. Tx of larger tumors should be managed rather in combination with other methods (e.g. $^{106}$Ru) in order to speed-up Tx and increase chances for total tumor regression.
3. Depending on clinical image and obtained therapeutic effects, Tx should be multiply repeated.
4. After TTT the cytotoxic effect gradually decreases proportionally to distance from central point of the diode laser spot with additional cell damage in the area adjacent to the necrotic zone.
5. The finding of an additional area of seriously injured cells may explain the prolonged time that is needed for tumor regression after TTT and the radiotherapeutic effect on this area in case of simultaneous plaque radiotherapy which may finally result in a deeper tumor necrosis compared to TTT as sole therapy.
6. All complications and side effects stated in the course of Tx were not dangerous to the eye, however in some cases further Tx may be problematic or even impossible.

**Additional comments on quality of study**

**Applicable?**

**Conclusions**

**Moderate**

**UNCLEAR (from abstract) if retrospective or prospective; directly applicable population, reasonable sized study, moderate follow-up**

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3. Depending on clinical image and obtained therapeutic effects, Tx should be multiply repeated.
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5. The finding of an additional area of seriously injured cells may explain the prolonged time that is needed for tumor regression after TTT and the radiotherapeutic effect on this area in case of simultaneous plaque radiotherapy which may finally result in a deeper tumor necrosis compared to TTT as sole therapy.
6. All complications and side effects stated in the course of Tx were not dangerous to the eye, however in some cases further Tx may be problematic or even impossible.

**Additional comments on quality of study**

**Moderate**

**UNCLEAR (from abstract) if retrospective or prospective; directly applicable population, reasonable sized study, moderate follow-up**
**Results**

- **Tx**: transpupillary thermotherapy (TTT) as primary Tx (Infrared diode laser at 810nm)
- **Population**: N=77 pts (77 eyes), selected choroidal melanoma. N=17 (22%) were parapapillary (PP) and N=60 (78%) were non-parapapillary (NPP) in location.
- **Follow-up (prospective)**: >36 mths (mean 55.2 +/- 17.9 mths in PP and 44.3 +/- 23.7 mths in NPP.

**RESULTS:**
- N=13 (76%) PP tumours and N=55 (92%) NPP tumours regressed (P>0.05).
- N=9 tumours recurred: n=7 were retreated using Iodine-125 brachytherapy and n=2 were enucleated (both parapapillary).
- Tumour thickness was predictive of recurrence (odds ratio: 4.3).
- Complications: n=20 (26%): macular pucker in 11 (14%), macular oedema in 3 (4%), retinal vein occlusion in 6 (8%), vitreous and subretinal haemorrhage in 2 (3%) and neovascular glaucoma in 3 (4%).
- PP tumours had more local complications (but NS; P>0.05).
- Complications = more frequent in tumours treated with >1 TTT session (P=0.01)
- Time-risk to develop intraocular complications was longer in the PP group (but NS; p=0.07).

**AUTHORS' CONCLUSION:** TTT may be a clinically effective method for conservative treatment of selected, non-parapapillary, small posterior choroidal melanoma.

**Additional comments on quality of study**
Prospective study; directly applicable population, fair sized study, long follow-up time.
RESULTS:
- End of follow-up: mean tumor thickness was reduced to 1.4 mm.
- TX success: N=94 eyes (94%) and failed in 6 eyes (6%).
- N=3 pts with amelanotic tumors showed no initial response to thermotherapy, but subsequent IV indocyanine green administration during thermotherapy resulted in improved heat absorption and tumor regression to a flat scar.
- N=6 eyes with Tx failure (N=4 eyes with tumors with partial or no response to thermotherapy, thus requiring plaque radiotherapy or enucleation, N=2 eyes with recurrence, subsequently controlled with additional thermotherapy).
- Visual acuity: same (within 1 line) or better than pre-Tx in 58 eyes (58%), worse in 42 eyes (42%).
- Main reasons for poorer vision: Tx through the foveola for subfoveal tumor (25 eyes), retinal traction (10 eyes), retinal vascular obstruction (5 eyes), optic disc edema (1 eye), and unrelated ocular ischemia (1 eye).
- Risks for retinal traction: temporal location (vs. nasal and superior, P=0.02), greater distance from the optic disc (P = 0.04).

AUTHORS’ CONCLUSIONS: Transpupillary thermotherapy may be an effective treatment for small posterior choroidal melanoma, especially those near the optic disc and fovea. Despite satisfactory local tumor control, ocular side effects can result in decreased vision. Longer follow-up will be necessary to assess the impact of thermotherapy on ultimate local tumor control and metastatic disease.

Additional comments on quality of study
- Prospective;
- Directly applicable population; Reasonable sample size, reasonable follow-up time

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### Results
- Tx: primary transpupillary thermotherapy; mean of 3 sessions.
- Population: N=256 pts with newly diagnosed choroidal melanoma; pre-Tx (means): tumor base 7.1 mm, tumor thickness 2.7 mm. Overlying subretinal fluid=84%, orange pigment on tumor surface=78%. All tumors showed either photographic documentation of growth (45%) or substantial risk factors for growth (55%).
- Methods: Unclear if retrospective or prospective
- Follow-up:
  - Complete tumor control without recurrence: N=232 (91%)
  - Recurrence: N=24 (9%).
  - Mean time to recurrence: 22 months
  - Mean recurrent tumor size: 3.8 mm base and 2.4 mm thick.
  - Additional thermotherapy in recurrent tumors: successful control N=13 (5%), plaque radiotherapy N=8 (3%), and enucleation N=3 (1%).
  - MULTIVARIATE (risk factors for tumor recurrence): increasing no. of thermotherapy sessions (reflecting less responsive tumor) (P = 0.0001) and optic disc overhung by tumor (P = 0.03).
  - 4% showed recurrence at 1 year, 12% at 2 years, and 22% at 3 years follow-up.
- In N=214 pts without multivariable risk factors for recurrence: recurrence = 2% at 1 year, 8% at 2 years, and 10% at 3 years.
- Visual acuity post-Tx: 20/20 to 20/40 (N=128, 50%), 20/50 to 20/100 (N=47, 18%), and 20/200 or worse (N=81, 32%).
- MULTIVARIATE (most SS at initial visit predictive of poor post-Tx visual acuity, worse or=20/200):
  1. documented tumor growth pre-Tx (P = 0.0001)
  2. mushroom tumor configuration (P = 0.002)
  3. initial symptom of blurred vision (P = 0.008)
  4. poor initial visual acuity (P = 0.005)
  5. superior quadrant tumor location (P = 0.03)
  6. underlying diabetes mellitus (P = 0.04)
  7. optic disc overhung by tumor (P = 0.04).
- Tumor-related mortality: N=2 pts (1%), one of whom showed complete tumor regression to thermotherapy and the other with diffuse choroidal melanoma and local tumor margin recurrence.

AUTHORS’ CONCLUSIONS: Transpupillary thermotherapy is an effective treatment for certain small choroidal melanomas. Appropriate tumor selection is critical to successful treatment. Patients with tumors abutting or overhanging the optic disc or those requiring more than three sessions for tumor control are more likely to develop ultimate tumor recurrence. Transpupillary thermotherapy can cause damaging effects to the retina, leading to visual loss shortly after treatment.

Additional comments on quality of study
Unclear if retrospective or prospective; Unclear if retrospective or prospective; directly applicable population; large sample size, reasonably long follow-up.

Primary transpupillary thermotherapy for small choroidal melanoma in 256 consecutive cases: outcomes and limitations

Study Type  Case Series
Number of patients  256 patients.
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
To evaluate ocular and systemic outcomes after primary transpupillary thermotherapy for choroidal melanoma and to identify the limitations of this treatment method.
Comparators
The treatment was delivered using a modified infrared diode laser at 810 nm with an adjustable beam width of 1.2 mm, 2.0 mm, and 3.0 mm. The infrared delivery system was adapted to a slit-lamp biomicroscope and delivered through a contact lens, as previously described. The thermotherapy parameters at each treatment session included infrared beam width (1.2 mm, 2.0 mm, 3.0 mm), power (mW), number of spots/tumor, and end point color change in the tumor. The use of indocyanine green enhancement was recorded.
Follow-up  Median: 16 months.
Outcomes recorded
Transpupillary thermotherapy is an effective treatment for certain small choroidal melanomas. Appropriate tumor selection is critical to successful treatment. Patients with tumors abutting or overhanging the optic disc or those requiring more than three sessions for tumor control are more likely to develop ultimate tumor recurrence. Transpupillary thermotherapy can cause damaging effects to the retina, leading to visual loss shortly after treatment.

The indications of primary TTT are limited. Patients must accept the high risk of local tumor recurrence.

Applicable? Transpupillary thermotherapy is an effective treatment for certain small choroidal melanomas.

Conclusions Appropriate tumor selection is critical to successful treatment. Patients with tumors abutting or overhanging the optic disc or those requiring more than three sessions for tumor control are more likely to develop ultimate tumor recurrence. Transpupillary thermotherapy can cause damaging effects to the retina, leading to visual loss shortly after treatment.

The indications of primary TTT are limited. Patients must accept the high risk of local tumor recurrence.

Additional comments on quality of study

Results

Complications of treatment included branch retinal vein obstruction in a vessel overlying the treated tumor in 104 eyes (41%), branch retinal artery obstruction in 31 (12%), retinal traction in 112 (44%), macular edema in 24 (9%), optic disc edema in 2 (<1%), neovascularization of the retina in 16 (6%), neovascularization of the optic disc in 0 (0%), and cataract in 2 (<1%).

Using Kaplan Meier estimates, 4% showed recurrence at 1 year, 12% at 2 years, and 22% at 3 years.

After treatment, the final visual acuity was 20/20 to 20/50 in 128 cases (50%), 20/50 to 20/100 in 47 cases (18%), and 20/200 or worse in 81 cases (32%).

One case of orbital melanoma recurrence was discovered in a patient with a juxtapapillary melanoma measuring 8.0 mm base and 3.4 mm thickness.

Applicable? Which choroidal melanoma should be treated with primary transpupillary thermotherapy? Our experience from 78 patients

Conclusions

509 Which choroidal melanoma should be treated with primary transpupillary thermotherapy? Our experience from 78 patients

Yarovoy AA, Magaramov DA, Bulgakova ES.

European Journal of Ophthalmology

20 186 193

Study Type Case Series

Number of patients

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable? Tx: TTT

Population: N=78 pts with choroidal melanomas; Tumor thickness up to 3.6 mm (mean 2.05 mm)

Follow-up: 2.5-108 months (mean, 32.8 months).

RESULTS:

- Tumour regression: N=51 (complete), N=20 (incomplete)
- No reponses: N=7 (N=2 had enucleation, N=5 Ru-106 irradiation)
- Recurrences after primary response: N=10 pts in 7-54 months (mean 23.4), N=8 after incomplete regression.
- N=6 recurrences successfully treated with additional TTT, N=4 with brachytherapy.
- N=0 metastases or deaths.
- Main predictive factors for TTT failure:
  1. Tumor height (OR 6.85; 95% CI=1.2-38.1; p=0.02)
  2. Basal diameter (OR 22.85; 95% CI=3.6-144.7; p=0.0003)
  3. Amelanotic pigmentation (for primary failure, OR 9.18; 95% CI=1.7-49.2; p=0.008)
  4. High maximum systolic velocity (for primary failure, OR13.6; 95% CI=2.3-81.7; p=0.003)
  5. Subretinal fluid (OR11.04; 95% CI=1.2-100.4; p=0.03)
  6. Incomplete regression (OR 30.62; 95% CI=6.0-156.4; p=0.00001).
- ROCs gave following cutoff levels: for tumor height 3.0 mm, for basal diameter 10.2 mm, for maximum systolic velocity 11.7 cm/s.
- Visual acuity (mean): Pre-TTT = 0.65, post-Tx = 0.58.
- 23% pts had increased visual acuity, 42% decreased acuity, and 35% no change.

AUTHORS’ CONCLUSIONS: TTT is an investigative treatment for choroidal melanomas. TTT needs careful selection of patients, based on consideration of predictive factors and functional perspectives.

Additional comments on quality of study
Retrospective study; directly applicable population, reasonably sized study, UNCLERF follow-up time.

Other

<table>
<thead>
<tr>
<th>Grading: 2+</th>
<th>Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</th>
</tr>
</thead>
</table>

3062 Relative survival rates after alternative therapies for uveal melanoma
Seddon JM, Gragoudas ES, Egan KM, Glynn RJ, Howard S, Fante RG, Albert DM. Ophthalmology

Study Type
<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patient Characteristics Inclusion/Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=556 pts (proton beam irradiation) vs. 238 patients (enucleation) vs. N=257 pts (previous enucleation)</td>
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</table>

Study aim/Intervention
- Irradiation vs. Enucleation vs. previous enucleation

Comparators
- Irradiation: median 5.3 yrs;
- Enucleation: median 8.8 yrs;
- previous enucleation: median 17.0 yrs

Follow-up
See below

Outcomes recorded
- All cause mortality (overall rate ratio): 1.2 (95% CI 0.9-1.6) fo concurrent enucleation vs. proton beam, and 1.6 (95% CI 1.2-2.1) for earlier enucleation vs. proton beam.
- Relative rates of metastatic death, cancer death, and all cause mortality comparing alternative treatments = varied with time after Tx.
- Proportional hazards: for all three outcomes, rate ratios were >2.0 and statistically significant for 1st 2 yrs post-Tx and closer to
AUTHORS' CONCLUSIONS: Results suggest that treatment choice has little overall influence on survival in patients with uveal melanoma.

Additional comments on quality of study: unable to determine all methodological aspects from abstract so have answered 'not reported' for many questions.

Grading: 3 Non-analytic studies (for example, case reports, case series)

1274 Influence of uveal melanoma therapy on patients' quality of life: a psychological study 2004

Chabert S, Velikay PM, Zehetmayer M. Acta Ophthalmologica Scandinavica 82 25 31

Study Type: Case Series

RESULTS:
- No significant differences in QoL (p=0.215) among treatments with different methods of radiotherapy.
- A decrease in QoL after radiotherapy.
- Average binocular visual acuity (VA) was 0.8 (range 0.3-1).
- Tx complications: reduction in VA in the affected eye, keratitis, cataract, scleral and corneal necrosis, radiation retinopathy, radiation optic neuropathy, retinal detachment and glaucoma.

AUTHORS' CONCLUSIONS: Due to the diagnosis revealed and the subsequent radiotherapy, patients with UM experienced a reduced QoL. However, compared to patients with other types of cancer, they seemed to feel relatively well and showed fewer signs of deterioration.

Additional comments on quality of study: Ok - but unclear length of follow-up (from abstract only) Ok sized study, directly applicable population, BUT unclear how long follow-up (seems short as just says 'after Tx')
Grading: 3 Non-analytic studies (for example, case reports, case series)

7728 Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma
Onken MD, Worley LA, Char DH, Augsburger JJ, Correa ZM, Nudleman E, Aaberg TMJ, Altaweel MM, Bardenstein DS, Finger PT, Gallie BL, Harocopos GJ, Hovland

Non-analytic studies (for example, case reports, case series) N=459 posterior UM Used: GEP vs “SNP tool” Median follow-up time was 17.4 years

Results:
- Metastasis was detected in 3 class 1 cases (1.1%) and 44 class 2 cases (25.9%)
- TNM staging
- An association between GEP class 2 and monosomy 3
- 54 of 260 tumors (20.8%) were discordant for GEP and chromosome 3 status

Claims:
The GEP provided a highly significant improvement in prognostic accuracy over clinical TNM classification and chromosome 3 status. Chromosome 3 status did not provide prognostic information that was independent of GEP.

(Kivela – response*)

Additional comments on quality of study
Prospective study; directly applicable population, large sized study, very long follow-up time.

8913 Chromosome 3 status in uveal melanoma: A comparison of fluorescence in situ hybridization and single-nucleotide polymorphism array
Singh AD, Aronow ME, Sun Y, Bebek G, Saunthararajah Y, Schoenfield LR, Biscotti CV, Tubbs RR, Triozzi PL, Eng C.
**Study Type**  Case Series

**Number of patients**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
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**Results**

Applicable? Conclusions

- N=50 UM treated by enucleation
- Used: FISH vs aSNP; sSNP (Illumina)
- Enucleation cases only
- Median follow-up time was 35.5 months

Results:
- 30 cases with monosomy 3 revealed by FISH
- 31 cases with chr 3 loss by aSNP
- 17 (52%) patients with mets & died
- No correlation with clinical or morphological features

Emphasis placed on cut-off of percentage of cells with monosomy 3 for definition (8-20%)

**Additional comments on quality of study**

- DIAGNOSTIC AND PROGNOSTIC; Retrospective; reasonable sample size; directly applicable population; reasonable follow-up time

**Study Type**  Case Series

**Number of patients**

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**Results**

Applicable? Conclusions

- N=374 UM patients treated by enucleation
- Enucleated (n=160)
- Endoresection (n=51)
- Biopsy (n=149)
- Median follow-up time = ? Longest 10 yrs

Results:
- 57 patients had died
- M3 significantly assoc with LBD

**Prognostic significance of chromosome 3 alterations determined by microsatellite analysis in uveal melanoma: a long-term follow-up study**


<table>
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<tr>
<th>Number of patients</th>
<th>Study Type</th>
<th>Case Series</th>
<th>Patient Characteristics</th>
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<th>Comparators</th>
<th>Follow-up</th>
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</table>

**Results**

- 57 patients had died
- M3 significantly assoc with LBD

**Additional comments on quality of study**

- DIAGNOSTIC AND PROGNOSTIC; Retrospective; reasonable sample size; directly applicable population; reasonable follow-up time
Variable proportion of M3 per specimen type. Since examining chrom. 8 using MSA.

**Additional comments on quality of study**

Retrospective study; directly applicable population, large sized study, very long follow-up time.

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<th>Study Type</th>
<th>Diagnostic</th>
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<tr>
<td>Number of patients</td>
<td>N=59 choroidal melanoma</td>
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<tr>
<td>Patient Characteristics</td>
<td>Used: FISH vs aSNP; aSNP (Illumina)</td>
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<tr>
<td>Study aim/Intervention</td>
<td>Biopsy cases only</td>
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<tr>
<td>Inclusion/Exclusion</td>
<td>? Median follow-up time</td>
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</table>

### Results

- ? patients with mets & died
- 49 (83%) of the cases yielded adequate DNA
- 38/59 (64%) cases with monosomy 3 revealed by FISH
- 43/59 (73%) cases with chr. 3 loss by aSNP

Additional chromosomes (e.g. 1, 4, 6, 9, 11, 16) examined using aSNP
Cut-off used for FISH not reported but 20% indicated from Fig. 1

**Additional comments on quality of study**

Directly applicable population; reasonable study size, unclear follow-up time (may be cross-sectional study)

### Grading: 4

**Expert opinion**

<table>
<thead>
<tr>
<th>7560</th>
<th>Molecular pathology of uveal melanoma</th>
<th>2013</th>
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</table>
FFPE - N=20 study of Enucleated eyes
Used GEP vs "MLPA"
TNM staging
"Blind" analysis
"LUMPO"
Class 1A, 1B, 2
MLPA – Minimal, Low, High
Median age 60 years
FU 16-50 months

Summary of Rv results/conclusions:
- Good correlation of results
- Some minor discrepancies of Class 1A and 1B groups
- 5 patients developed mets: all identified as "high-risk" by both methods

Additional comments on quality of study
Letter to editor reviewing published studies

Grading: 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2721 The prognostic value of tumor blood vessel morphology in primary uveal melanoma 1993
Folberg R, Rummelt V, Parys VG, Hwang T, Woolson RF, Pe'er J, Gruman LM, Ophthalmology 100 1389 1398
### Applicable?

**Conclusions**

**Additional comments on quality of study**

RACHEL COMMENT: Abstract

only gives results of the cases

### Grading: 3 **Non-analytic studies (for example, case reports, case series)**

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</table>

Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis

1982

McLean IW, Foster WD, Zimmerman LE,

*Human Pathology*

13 123 132

### Study Type

- **Case Series**

### Additional comments on quality of study

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

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<thead>
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</table>

Uveal melanoma. Comparison of the prognostic value of fibrovascular loops, mean of the ten largest nucleoli, cell type, and tumor size

1997

McLean IW, Keefe KS, Burnier MN,

*Ophthalmology*

104 777 780
Grading: 3 Non-analytic studies (for example, case reports, case series)

111 Immunohistochemical assessment of mitotic count in uveal melanoma 2011
### Study Type
Case Series

#### Number of patients
- Patient Characteristics
  - Study aim/Intervention
  - Comparators
  - Follow-up
  - Outcomes recorded

#### Results

#### Applicable?

#### Conclusions

#### Additional comments on quality of study

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### Study Type
Case Series

#### Number of patients
- Patient Characteristics
  - Study aim/Intervention
  - Comparators
  - Follow-up
  - Outcomes recorded

#### Results

#### Applicable?

#### Conclusions

#### Additional comments on quality of study

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### Study Type
Case Series

#### Number of patients
- Patient Characteristics
  - Study aim/Intervention
  - Comparators
  - Follow-up
  - Outcomes recorded

#### Results

#### Applicable?

#### Conclusions

#### Additional comments on quality of study

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Tumor-infiltrating macrophages (CD68(+) cells) and prognosis in malignant uveal melanoma


Study Type: Case Series

Number of patients: 1788

Results

Microcirculation and tumor-infiltrating macrophages in choroidal and ciliary body melanoma and corresponding metastases


Study Type: Case Series

Number of patients: 1399

Results
### Analysis of intraocular biopsies. [Review]

**2012**

Coupland SE, Developments in Ophthalmology

<table>
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<tr>
<th>Study Type</th>
<th>Patient Characteristics</th>
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<th>Comparators</th>
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### Results

Applicable?

Conclusions

Additional comments on quality of study

Grading: 4 *Expert opinion*

<table>
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<th>Grading</th>
<th>Study Type</th>
<th>Number of patients</th>
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</table>

Non-analytic studies (for example, case reports, case series)

Grading: 3 *Non-analytic studies (for example, case reports, case series)*
N=452 UM involving choroid
Median follow-up time was 1.89 years
Used MLPA

Results:
- 57 patients had died
- Significantly assoc with:
  - LBD
  - Monosomy 3
  - Polysomy 8q
  - Combination of both
  - Epithelioid cellularity
  - High mitotic count
  - Closed loops

Ten-year disease-specific mortality was 0% in 133 tumors with no chromosome 3 loss, 55% in tumors with chromosome 3 loss but no chromosome 8q gain, and 71% in 168 tumors showing combined chromosome 3 loss and 8q gain.

Additional comments on quality of study
Prognostic
Retrospective; directly applicable population; very large study size, fair follow-up time
### Results

- 76 patients had died
- Significantly assoc btwn M3 and:
  - Increasing LBD
  - CB involvement
  - Epithelioid cellularity

Monosomy 3 was present in 23% of small UM (<10 mm in diameter)
15% false negative rate

### Additional comments on quality of study

Large study, retrospective, directly applicable population; reasonable follow-up

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<th>Study Type</th>
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<tr>
<td>Number of patients</td>
<td>Patient Characteristics Inclusion/Exclusion Study aim/Intervention Comparators Follow-up Outcomes recorded</td>
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<tr>
<td>416</td>
<td>Frequent mutation of BAP1 in metastasizing uveal melanomas</td>
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</table>

### Additional comments on quality of study

Experimental

Loss of heterozygosity of chromosome 3 detected with single nucleotide polymorphisms is superior to monosomy 3 for predicting metastasis in uveal melanoma

<table>
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<tr>
<th>Study Type</th>
<th>Experimental</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>Patient Characteristics Inclusion/Exclusion Study aim/Intervention Comparators Follow-up Outcomes recorded</td>
</tr>
<tr>
<td>900</td>
<td>Loss of heterozygosity of chromosome 3 detected with single nucleotide polymorphisms is superior to monosomy 3 for predicting metastasis in uveal melanoma</td>
</tr>
</tbody>
</table>
### Results

**Applicable?**
N=53 UM; Fresh samples

**Conclusions**
Used: SNP-custom designed (28 SNPs - n=53); FISH n=28; aCGH n=45  
FU period: 25 months

Results:
- Metastatic deaths in low risk:
  - 10% with their SNP analysis,
  - 25% with aCGH,
  - 35% with FISH

Lab-based SNP tool has not been externally validated

Was a “proof-of-principle” study

**Additional comments on quality of study**
Dx and prognostic; retrospective study; reasonable sample size; directly applicable population; reasonable follow-up;

### Additional comments on quality of study

An accurate, clinically feasible multi-gene expression assay for predicting metastasis in uveal melanoma

Onken MD, Worley LA, Tuscan MD, Harbour JW,

Journal of Molecular Diagnostics

2010 12 461 468

**Study Type**
Case Series

**Number of patients**

**Patient Characteristics**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

### Results

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

Experimental and prognostic
Results:
- 12 developed mets
- Monosomy 3 strong risk factor for metastatic spread

Two gene sets compared for GEP
Both subdividing into two groups using clustering techniques
Important paper showing prognostic role of monosomy 3 in OCM (p<0.0001). Small sample size with highly significant p value suggesting important role for ts genes on chr 3.

N=54 UM pts
Median FU = 3.4 yrs
Fresh samples

RESULTS:
- 17 (57%) had loss of chromosome 3
- No patient deaths in disomy 3 tumours
Univariate analysis:
- Monosomy 3 strongest predictor of metastasis; followed by tumour location and LBD

No additional value of age, sex, EOM, tumour thickness

Applicable?

Conclusions

Prospective study; directly applicable population, smallish study, reasonable follow-up time.

Study Type
Case Series

Number of patients
N=140 UM

Patient Characteristics
Used MSA

Study aim/Intervention
Median follow-up time = 8 months

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

923 Chromosome 3 analysis of uveal melanoma using fine-needle aspiration biopsy at the time of plaque radiotherapy in 140 consecutive cases: the Deborah Iverson, MD, Lectureship

Results:
- M3 in 44 cases (31%)
- D3 in 76 cases (54%)
- Insufficient yield in 20 (14%)
- M3 found in both small & large UM
- M3 significantly assoc with:
  - LBD
  - Distance from the disc
Multiplex ligation-dependent probe amplification equals fluorescence in-situ hybridization for the identification of patients at risk for metastatic disease in uveal melanoma

Vaarwater J, Van Den BT, Mensink HW, Van KC, Verdiak RM, Naus NC, Paridaens D. Melanoma Research Bruggenwirth HT, Kilic E, de KA.

Study Type
Diagnostic

Number of patients
64 UM; Fresh samples

Used: MLPA vs FISH (n=64); aSNP (n=7)

Median follow-up time: 1.89 yrs

Results:
- Loss of chromosome 3, loss or gain of 8p, and gain of 8q, found with MLPA, correlated with a significantly lower disease-free survival (P<0.001)
- Sensitivity of MLPA to detect patients at risk for metastatic disease was higher than that of FISH (0.795 vs. 0.692) but the specificity was equal for both techniques (0.840).

Additional comments on quality of study
Diagnostic

Dx and prognostic; retrospective, reasonable sample size, directly applicable population; fair follow-up.

Grading:
2+

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Circulating melanoma cells in peripheral blood of patients with uveal melanoma before and after different therapies and association with prognostic parameters: a pilot study

Suesskind D, Ulmer A, Schiebel U, Fierlbeck G, Spitzer B, Spitzer MS, Bartz SK, Grisanti S.

Study Type
Cohort

Number of patients
89 17 24

Acta Ophthalmologica

Study aim/Intervention
Inclusion/Exclusion
Grading:  3  Non-analytic studies (for example, case reports, case series)

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**Results**

Applicable?  
Conclusions  

Additional comments on quality of study  
Diagnostic markers but not sens/spec Dx study
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**Additional comments on quality of study**
Prognostic

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**Additional comments on quality of study**
Prognostic

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<td>Conclusions</td>
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</tbody>
</table>

**Additional comments on quality of study**
Prognostic
METHOD: conditional hazard estimating neural network (CHENN)

POPULATION: Choroidal melanoma pts - treated. 1. training set N= 1780; 2. test set N= 874 pts

Follow-up: not stated in abstract

RESULTS:
- All-cause survival curves generated by the CHENN matched those produced with Kaplan-Meier analysis (P<0.05).
- In older pts, however, the estimated melanoma-related mortality was lower with the CHENN, which accounted for competing risks, unlike Kaplan-Meier analysis.

Comment: Estimation of survival prognosis in patients with choroidal melanoma requires multivariate assessment of age, sex, clinical tumor stage, cytogenetic melanoma type, and histologic grade of malignancy.

Additional comments on quality of study

Applicable?

Conclusions

1166 Forecasting the prognosis of choroidal melanoma with an artificial neural network 2005
Kaiserman I, Rosner M, Pe’er J, Ophthalomology 112 1608

Study Type

Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

Population: N=153 choroidal melanoma (age, 58.4+/-14.6 years) had ruthenium 106 brachytherapy
Method: ANN
Follow-up: 5 years

RESULTS:
Outcome measure: ability of the ANNs to forecast the 5-year mortality from choroidal melanoma
- logistic regression reached 86% forecasting accuracy, with a very low LR (0.8), whereas the human expert forecasting ability was <70% (LR, 1.85)

No genetics included

Additional comments on quality of study

Also diagnostic data and prognostic
Retrospective; directly applicable population; large sample size; long follow-up.

1393 Modelling survival after treatment of intraocular melanoma using artificial neural networks and Bayes theorem 2004
Population: intraocular melanoma; N=2331, split randomly into training and test sets
Method: ANN / AI
Follow-up: 10 and 15 years

RESULTS: For outcome of metastatic death, AI system can match if not better the clinical expert's prediction

Results

Applicable? Conclusions
Population: intraocular melanoma; N=2331, split randomly into training and test sets
Method: ANN / AI
Follow-up: 10 and 15 years

RESULTS: For outcome of metastatic death, AI system can match if not better the clinical expert's prediction

Additional comments on quality of study
Validation study of an AI system
Retrospective; directly applicable population; huge sample size; very long follow-up.

Grading: 4 Expert opinion

138 Estimating prognosis for survival after treatment of choroidal melanoma. 2011
Damato B, Eleuteri A, Taktak AF, Coupland SE, Progress in Retinal & Eye Research 30 285 295

Study Type Review
Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded
Results

Applicable? Conclusions

Additional comments on quality of study
### Reactions to and desire for prognostic testing in choroidal melanoma patients

**Beran TM, McCannel TA, Stanton AL, Straatsma BR, Burgess BL,**

*Journal of Genetic Counseling*

**2009 Jun**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tr>
<td>Qualitative</td>
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#### Results

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<th>Study aim/Intervention</th>
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</table>

#### Additional comments on quality of study

526

### Psychological aspects of cytogenetic testing of uveal melanoma: preliminary findings and directions for future research

**Cook SA, Damato B, Marshall E, Salmon P,**

*Eye*

2009

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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#### Results

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</tbody>
</table>
Applicable?
Conclusions

Additional comments on quality of study
### Extractions for Question: Should all patients be offered surveillance?

**Grading:** 2++  
*High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal*

<table>
<thead>
<tr>
<th>Study Type</th>
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<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>Systematic Review</td>
<td>Small, retrospective case series 31/4222</td>
<td></td>
<td></td>
<td>Variable</td>
<td></td>
<td>Differing strategies</td>
</tr>
</tbody>
</table>

**Results**
- Levels of specific biomarkers reported when metastasis was first confirmed (n = 14)
- % of patients with abnormal results on surveillance testing (n=13)
- Values of diagnostic markers assoc. with surveillance regimen (7)
- Survival time after metastasis detection (7)
- Total survival time after initial diagnosis/Tx (3)
- % of patients whose metastatic tumors were detected by presymptomatic testing (5)
- Surveillance regimens employed by different groups (1)
- Relationship with other prognostic factors for UM metastasis (1)

**Applicable?**  
Failed to find a survival benefit assoc. with regular surveillance

**Conclusions**
- No RCT performed

### Additional comments on quality of study

**8963**  
**Study:** Surveillance testing for metastasis from primary uveal melanoma and effect on patient survival  
**Year:** 2011  
**Authors:** Augsburger JJ; Correa ZM; Trichopoulos N  
**Journal:** American journal of ophthalmology  
**Patients:** 152  
**Follow-up:** 5  
**Outcomes:** 9

**9110**  
**Study:** MRI in the detection of hepatic metastases from high-risk uveal melanoma: a prospective study in 188 patients  
**Year:** 2013  
**Authors:** Marshall E, Romaniuk C, Ghaneh P, Wong H, McKay M, Chopra M, Coupland SE, Damato BE  
**Journal:** The British journal of ophthalmology  
**Patients:** 97  
**Follow-up:** 159  
**Outcomes:** 163
### Detection of asymptomatic hepatic metastases from uveal melanoma

<table>
<thead>
<tr>
<th>Study Type</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>188 pts</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>90 pts with mets</td>
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<tr>
<td>Study aim/Intervention</td>
<td>Detection of asymptomatic hepatic metastases from uveal melanoma</td>
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<tr>
<td>Comparators</td>
<td>Median FU of 28.8 months</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Study closure @ 5yrs</td>
</tr>
<tr>
<td>Outcomes recorded</td>
<td>MRI of high risk pts</td>
</tr>
</tbody>
</table>

#### Results

- 92% asymptomatic
- 38 operable on MRI
- R0 resection in 12 pts
- 35% pts survived 5 yrs

### Conclusions

Hepatic MRI has made it possible to evaluate treatments for metastases at an earlier stage of disease.

### Additional comments on quality of study

Grading: 3 Non-analytic studies (for example, case reports, case series)

<table>
<thead>
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<tr>
<td>Number of patients</td>
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<td>Inclusion/Exclusion</td>
<td>1985-1996</td>
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<td>CXR</td>
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<td>Follow-up</td>
<td>Abdom US</td>
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<tr>
<td>Outcomes recorded</td>
<td></td>
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</tbody>
</table>

#### Results

- 59% with mets asymptomatic
- 80% hepatic mets only

### Conclusions

- Recommends biannual screening
- Combination of US and LFTs
- CXR of no use

### Additional comments on quality of study

cohort retrospective
<table>
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<th>Study Type</th>
<th>Case Series</th>
<th>Number of patients</th>
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<th>2000-2005</th>
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<tr>
<td>Patient Characteristics</td>
<td>Inclusion/Exclusion</td>
<td>Study aim/Intervention</td>
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<tr>
<td>Study Type</td>
<td>Case Series</td>
<td>Comparators</td>
<td>MRI</td>
<td>5.2 + 1.7 years (range, 1.2–6.6 yrs)</td>
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<td>Number of patients</td>
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<td>Follow-up</td>
<td>Biopsy/resection</td>
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<td></td>
<td>Outcomes recorded</td>
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<td></td>
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<tr>
<td>Results</td>
<td>13% with asymptomatic abnormalities; 9% proven mets</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Applicable?</td>
<td>Resulted in initiation of Tx</td>
<td></td>
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<tr>
<td>Conclusions</td>
<td>No improved survival</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Additional comments on quality of study</td>
<td></td>
<td></td>
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</tbody>
</table>
If so, what is a high-risk and or low-risk uveal melanoma?

Grading: 3 Non-analytic studies (for example, case reports, case series)

123 The biology of micrometastases from uveal melanoma 2011
Jager MJ, Cree IA,

Study Type Case Study
Number of patients 
Patient Characteristics Study aim/Intervention Comparators
Inclusion/Exclusion

Results

Applicable? Conclusions
Aim: causes of tumour latency in UM
METHODS: postmortem analysis of micrometastases in liver tissue (immunohistochemistry and detection of marker genes by PCR)
POPULATION: N=22 pts with UM who died (N=196 possible enrolled)

RESULTS:
- N=16/22 pts died with large deposits of metastatic melanoma, N=6 died of other causes.
- N=1 pt had no clinical evidence of metastasis.
- Metastatic melanoma cells were identified by: immunohistochemistry (N=1), qRT-PCR (N=4 pts without macrometastases).
- No evidence of multicellular micrometastases sufficiently large to require angiogenesis
- No associated inflammation was observed.

AUTHORS' CONCLUSION: The most likely explanation for latency in this setting is the inability of uveal melanoma cells in metastatic sites to grow

Additional comments on quality of study
Directly applicable population, Small sample size (but reasonable given post-mortem analysis of tissue, and donor consent required)

2939 Survival of patients with metastases from uveal melanoma 1991 Mar
Gragoudas ES, Egan KM, Seddon JM, Glynn RJ, Walsh SM, Finn SM, Munzenrider JE, Spar MD,

Study Type Case Series
Number of patients
Patient Characteristics Study aim/Intervention Comparators
Inclusion/Exclusion

Outcomes recorded
N=145 pts with metastatic UM after proton beam irradiation.
Aim: to assess the effect of early Dx and Tx for metastases on survival.
Metastases were Dx between 7 wks and 8.3 yrs (median, 2.4 years) after proton beam irradiation.

RESULTS:
- Most pts (n = 94) were symptomatic before Dx; the others were detected during screening examination.
- Liver involvement = nearly all pts (n = 136).
- Most pts had died from metastases by the close of the study (n = 137).
- Survival significantly longer for pts Dx during screening exam (P = 0.004) and in young patients (P = 0.03).
- Most pts received some form of Tx for metastases (69%).
- Median survival = 2.0 mths for pts with no Tx vs. 5.2 mths for pts who had Tx for metastases (P = .0001).
- However, overall 1-year survival rate was poor (13%).

AUTHORS’ CONCLUSIONS: Prophylactic adjuvant therapy could be explored as a means to increase disease-free survival in pts with UM.

### Additional comments on quality of study

**Study Type** Diagnostic

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patient Characteristics</th>
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<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>12 metastatic patients. Prevalence not stated</td>
<td>PET CT</td>
<td>CT not compared</td>
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</table>

**Results**
PET positivity helpful in equivocal lesions

**Applicable? Conclusions**
no relates to optimal staging question: PET can identify metastatic disease but comparative studies not performed.
### Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

<table>
<thead>
<tr>
<th>Grading</th>
<th>2+</th>
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<tbody>
<tr>
<td><strong>Histomorphological</strong></td>
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</table>

**The morphologic characteristics of tumor blood vessels as a marker of tumor progression in primary human uveal melanoma: a matched case-control study**

Folberg R, Pe'er J, Gruman LM, Woolson RF, Jeng G, Montague PR, Moninger TO, Yi H, Moore KC,

**Human Pathology**

1992 Nov

<table>
<thead>
<tr>
<th>Study Type</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<td>Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</td>
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<td>Outcomes recorded</td>
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</table>

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

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<tr>
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<tbody>
<tr>
<td>Number of patients</td>
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<tr>
<td>Patient Characteristics</td>
<td>AgNOR values in Callender histopathological types of malignant uveal melanomas</td>
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<td>Inclusion/Exclusion</td>
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<td>1995 Jul</td>
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<td>2535</td>
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**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**
<table>
<thead>
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<th>Grading:</th>
<th>3</th>
<th>Non-analytic studies (for example, case reports, case series)</th>
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<tbody>
<tr>
<td>1413</td>
<td>Nucleolar diameter and microvascular factors as independent predictors of mortality from malignant melanoma of the choroid and ciliary body</td>
<td>2003</td>
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<td>Al JRT, Makitie T, Kivela T,</td>
<td>Investigative Ophthalmology and Visual Science</td>
<td>44 2381 2389</td>
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<tr>
<td>Study Type</td>
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<td>Outcomes recorded</td>
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</table>

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

<p>| 2370 | Uveal melanomas: Relationship with histological type, size, nuclear DNA content, nucleolar organizer regions and proliferating cell nuclear antigen | 1996 |</p>
<table>
<thead>
<tr>
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**Results**

- **Applicable?**
- **Conclusions**

**Additional comments on quality of study**

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**Results**

- Tx:variable - see results
- Population: N= 2256 pts with UM (n=67 / 3% pts had extraocular extension.
- Methods: Retrospective study
- Follow-up: median = 38 (range 7 to 79) mths

**RESULTS:**

- Eye-conserving Tx used: n=38 (52.8%) pts.
- Enucleation in 29 (47.2%) pts.
- Overall survival rate (5 years): 40.4% in enucleated patients and 79.3% in the eye-conserving treatment group (protons n=19, iodine-125 plaque n=19) (p=0.01; Kaplan-Meier analysis).
- Tumour recurrence: none in any group.
- Choice of Tx was influenced by: degree of extraocular spread as well as the clinical characteristics tumour location, retinal detachment, ciliary body involvement (p<0.01; chi(2) test) and tumour thickness (p=0.04; chi(2) test).
- Age, tumour diameter, involvement of optic nerve, vitreous haemorrhage and the amount of pigment did not have any influence.
AUTHORS' CONCLUSIONS: Tumour recurrence rates and survival rates were not adversely affected in patients receiving conservative eye treatment. This may thus represent a therapeutic option in certain patients with extraocular spread.

<table>
<thead>
<tr>
<th>Additional comments on quality of study</th>
<th>RETROSPECTIVE Comparing outcome after different primary treatments in those with metastatic disease</th>
</tr>
</thead>
</table>

**2372**  Irradiated uveal melanomas: cytopathologic correlation with prognosis 1996 Oct
Char DH, Kroll SM, Miller T, Castro J, Quivey J, American Journal of Ophthalmology 122 509 513

<table>
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<td>Comparators</td>
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<td>Follow-up</td>
<td>Outcomes recorded</td>
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</table>

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

**2376**  Prognostic value of morphometric features and the callender classification in uveal melanomas. 1996 Oct
Coleman K, Baak JP, van Diest PJ, Mullaney J, Ophthalmology 103 1634 1641

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<thead>
<tr>
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</table>
Results

<table>
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<tr>
<th>Applicable?</th>
<th>Conclusions</th>
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</table>

Additional comments on quality of study

2395  Microvessel count predicts survival in uveal melanoma  1996 Jul 1

Study Type  Case Series
Number of patients  123 evaluable patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results  Microvessel density(p<0.0005) and tumour size predicted poor outcome on multivariate analysis.

2838  A comparison of prognostic covariates for uveal melanoma  1992 May

Applicable?  Antiangiogenics currently under study in SUAVE trial.
Conclusions

Additional comments on quality of study
A simple cytologic method for predicting the malignant potential of intraocular melanoma

Huntington A, Haugan P, Gamel J, McLean I,
Pathology, Research & Practice
185 631 634

Study Type: Case Series
Number of patients: 3119

Results

Applicable?
Conclusions

Additional comments on quality of study
Study Type: Case Series
Number of patients

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

Additional comments on quality of study

Microvascular loops and networks as prognostic indicators in choroidal and ciliary body melanomas

Makitie T, Summanen P, Tarkkanen A, Kivela T,

Journal of the National Cancer Institute

1999 Feb 17

2042

Number of patients

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

Additional comments on quality of study

Uveal melanoma. The importance of large nucleoli in predicting patient outcome - An Automated Image Analysis Study

McLean IW, Sibug M, Becker RL, McCurdy JB,

Cancer

1997

2308

Study Type: Case Series
Number of patients

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

Additional comments on quality of study
3368  Prognostic factors in choroidal and ciliary body melanomas with extrascleral extension
1986 Mar 15
Pach JM, Robertson DM, Taney BS, Martin JA, Campbell RJ, O'Brien PC,
American Journal of Ophthalmology 101 325 331

Study Type: Case Series
Number of patients
Patient Characteristics
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results

Applicable?
Conclusions

Additional comments on quality of study

616  What is the significance of vortex vein invasion in uveal melanoma?
2009 Aug
Raoof N, Rennie IG, Salvi SM, Sisley K, Caine A, Mudhar HS,
Eye 23 1661 1667

Study Type: Case Series
Number of patients
Patient Characteristics
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results

Applicable?
Conclusions

Additional comments on quality of study

Prognostic
### Microcirculation architecture of metastases from primary ciliary body and choroidal melanomas

**Study Type:** Case Series  
**Number of patients:** 2196  
**Comparators:**  
**Follow-up:**  
**Outcomes recorded:**  

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study** Experimental study

---

### Histologic findings and prognosis of uveal malignant melanoma in Japanese patients

**Study Type:** Case Series  
**Number of patients:** 2448  
**Comparators:**  
**Follow-up:**  
**Outcomes recorded:**  

**Results**

**Applicable?**

**Conclusions**
### Additional comments on quality of study

<table>
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<th>Study Type</th>
<th>Number of patients</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<td>Case Series</td>
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#### Results

**Applicable?**

**Conclusions**

### Additional comments on quality of study

<table>
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<th>Study Type</th>
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</table>

#### Results

**Applicable?**

**Conclusions**
Results

Prognostic value of nucleolar size and size pleomorphism in choroidal melanomas 1993 May
Sorensen FB, Gamel JW, Jensen OA, Ladekarl M, McCurdy J, APMIS 101 358 368

Study Type: Case Series

Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention

Comparators
Follow-up
Outcomes recorded

Results

Prognostic features of uveal malignant melanoma 1995

Grading: 4 Expert opinion

2532 Prognostic features of uveal malignant melanoma 1995
<table>
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Results

Applicable?

Conclusions

Additional comments on quality of study
### Immunohistochemical Grading:

| Grading | Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal |

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**Study Type**: Cohort

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

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**Study Type**: Case-Control

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**
### Additional comments on quality of study

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**Grading:** 3  
**Non-analytic studies (for example, case reports, case series)**

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<td>2238</td>
<td>Human leukocyte antigen class I expression: Marker of poor prognosis in uveal melanoma</td>
<td>1997</td>
<td>38 1865 1872</td>
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**Results**

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<td>Case Series</td>
<td>1594</td>
<td>p53 Immunoreactivity, Ki-67 expression, and microcirculation patterns in melanoma of the iris, ciliary body, and choroid</td>
<td>2002 Feb</td>
<td>24 105 108</td>
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</table>
Association of HLA class I and class II antigen expression and mortality in uveal melanoma


1745 2001 Sep

Additional comments on quality of study
### Comparison of uveal melanoma growth rates with mitotic index and mortality

**Gass JD**, *Archives of Ophthalmology* 103 924 931

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**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

### Role of macrophages in uveal melanoma


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**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

Experimental study as well as prognostic
HLA class II antigen expression in uveal melanoma: correlation with clinicopathological features

Krishnakumar S, Abhyankar D, Lakshmi SA, Shanmugam MP, Pushparaj V, Biswas J
Experimental Eye Research

Study Type: Case Series
Number of patients: 1507
Patient Characteristics: Inclusion/Exclusion
Study aim/Intervention: 
Comparators: 
Follow-up: 
Outcomes recorded: 77 175 180

Results

Applicable?
Conclusions

Additional comments on quality of study

Major histocompatibility antigens and antigen-processing molecules in uveal melanoma

Krishnakumar S, Abhyankar D, Sundaram AL, Pushparaj V, Shanmugam MP, Biswas J
Clinical Cancer Research

Study Type: Case Series
Number of patients: 1509
Patient Characteristics: Inclusion/Exclusion
Study aim/Intervention: 
Comparators: 
Follow-up: 
Outcomes recorded: 9 4159 4164

Results

Applicable?
Conclusions

Additional comments on quality of study
2521  Cell cycling and prognosis in uveal melanoma  1995 Jan
Lattman J, Kroll S, Char DH, Ghazvini S, Frigillana H, O’Brien JM, Elbakri HR,  Clinical Cancer Research  1  41  47

Study Type  Case Series
Number of patients
Patient Characteristics  Study aim/Intervention
Comparators
Follow-up  Outcomes recorded

Results

Applicable?
Conclusions

Additional comments on quality of study

614  Blood vessel maturation in human uveal melanoma: spatial distribution of neovessels and mature vasculature  2009

Study Type  Case Series
Number of patients
Patient Characteristics  Study aim/Intervention
Comparators
Follow-up  Outcomes recorded

Results
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**Results**

Applicable?  
Conclusions

**Additional comments on quality of study**  
Prognostic
### Genetic

**Grading:** 2+  
**Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal**

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- **2047**  
  Frequent loss of heterozygosity on chromosome 6p in uveal melanoma
- **1999**
  Metzelaar BJAW, Jager MJ, Moghaddam PH, van der Slik AR, Giphart MJ, *Human Immunology*  
  60 962 969

**Study Type**  
Case-Control

**Number of patients**  
Patient Characteristics
Inclusion/Exclusion

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

### Conclusions

Additional comments on quality of study

### Grading: 3  
**Non-analytic studies (for example, case reports, case series)**

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- **1704**  
  Concomitant loss of chromosome 3 and whole arm losses and gains of chromosome 1, 6, or 8 in metastasizing primary uveal melanoma
- **2001 Feb**
  42 313 317

**Study Type**  
Case Series

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Patient Characteristics
Inclusion/Exclusion

**Study aim/Intervention**

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**Outcomes recorded**

### Additional comments on quality of study
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<td>675</td>
<td>FISH analysis of chromosomes 3 and 6 on fine needle aspiration biopsy samples identifies distinct subgroups of uveal melanomas</td>
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**Results**

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<tr>
<td>Number of patients</td>
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<tr>
<td>127</td>
<td>Effect of heterogeneous distribution of monosomy 3 on prognosis in uveal melanoma</td>
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<td></td>
<td>Bronkhorst IHG, Maat W, Jordanova E.S., Kroes WGM, Schalij DNE, Luyten GPM, Jager MJ,</td>
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</table>
Multiplex ligation-dependent probe amplification of uveal melanoma: correlation with metastatic death

544
Damato B, Dopierala J, Klaasen A, van DM, Sibbring J, Coupland SE,
Investigative Ophthalmology & Visual Science

Results

N=73 treated UM; Mean age: 60 yrs; Fresh samples, Enucleation or resection
Used: MLPA (n=73); FISH (n=9)
Median FU = 6.2 yrs

Results:
- Metastatic death in 28 pts
- Correlated with M3 and P8
- Chrom 1,3,6,8
- Partial deletions detected with MLPA not seen with FISH
- Significance of partial deletions and borderline alterations of chrom. 3

Additional comments on quality of study
Prognostic
Retrospective; directly applicable population; reasonable study size, long follow-up time
### Comparative genomic hybridization analysis of archival formalin-fixed paraffin-embedded uveal melanomas

**Ghazvini S, Char DH, Kroll S, Waldman FM, Pinkel D,** Cancer Genetics & Cytogenetics 90 95 101

<table>
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#### Additional comments on quality of study

### Loss of heterozygosity of 1p in uveal melanomas with monosomy 3


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Loss of chromosome 3 alleles and multiplication of chromosome 8 alleles in uveal melanoma

Horsthemke B, Prescher G, Bornfeld N, Becher R, Genes, Chromosomes & Cancer

1992 Apr

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Microarray comparative genomic hybridisation analysis of intraocular uveal melanomas identifies distinctive imbalances associated with loss of chromosome 3

Hughes S, Damato BE, Giddings I, Hiscott PS, Humphreys J, Houlston RS, British Journal of Cancer

2005 Nov 14

<table>
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Concurrent loss of chromosome arm 1p and chromosome 3 predicts a decreased disease-free survival in uveal melanoma patients


Study Type: Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Whole-genome microarray detects deletions and loss of heterozygosity of chromosome 3 occurring exclusively in metastasizing uveal melanoma

Lake SL, Coupland SE, Taktak AF, Damato BE, Investigative Ophthalmology & Visual Science

Study Type: Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results
Multiplex ligation-dependent probe amplification analysis of uveal melanoma with extraocular extension demonstrates heterogeneity of gross chromosomal abnormalities


Study Type Case Series
Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Cytogenetics and prognosis for uveal melanoma in Korean patients

Lee CS, Lee J, Choi JJ, Yang WI, Yoon JS, Lee SY, Lee SC, Acta Ophthalmologica 89 e310 e314

Study Type Case Series
Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded
Applicable?

Conclusions

Additional comments on quality of study

RESULTS:
- N=0 postoperative endophthalmitis, orbital dissemination, or local treatment failure.
- N=3 rhegmatogenous retinal detachment. F
- N=14 clinical evidence of metastasis (n=8 monosomy 3 of the primary tumor; n=2 disomy 3; n=1 had trisomy 3; n=3 had insufficient material for FISH).
- 5-year metastatic rate = 13%.

AUTHORS’ CONCLUSIONS: Transscleral FNAB at the time of iodine-125 plaque brachytherapy was not associated with endophthalmitis, orbital dissemination, or local treatment failure in this series, and post-brachytherapy retinal detachment occurred in 3 eyes. The cumulative KaplanMeier 5-year metastatic rate was not statistically different from the rate of 13% reported by the Collaborative Ocular Melanoma Study for tumors of the same size treated by brachytherapy without biopsy. Rhegmatogenous retinal detachment may occur in young patients secondary to posterior vitreous detachment induced by tumor response to radiation, unrelated to FNAB.
### Additional comments on quality of study

Retrospective study; directly applicable population, reasonably sized study, long follow-up time.

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**Results**

**Applicable?**

**Conclusions**

### Additional comments on quality of study

#### Assessment of chromosome 3 copy number in ocular melanoma using fluorescence in situ hybridization

McNamara M, Felix C, Davison EV, Fenton M, Kennedy SM, Cancer Genetics & Cytogenetics 98 4 8

- **Study Type**: Case Series
- **Results**: 2310
- **Number of patients**: 2310
- **Patient Characteristics**: 
- **Inclusion/Exclusion**: 
- **Study aim/Intervention**: 
- **Comparators**: 
- **Follow-up**: 
- **Outcomes recorded**: 

### Additional comments on quality of study

#### Chromosome 3 intratumor heterogeneity in uveal melanoma


- **Study Type**: Diagnostic
- **Number of patients**: 598
- **Patient Characteristics**: 
- **Inclusion/Exclusion**: 
- **Study aim/Intervention**: 
- **Comparators**: 
- **Follow-up**: 
- **Outcomes recorded**: 

### Additional comments on quality of study

**Applicable?**

**Conclusions**

**Experimental study**
N=32 posterior UM undergoing plaque brachytherapy
Used FISH
FNAB
Median FU = 47 months

Results:
- Mean LBD = 12.5mm
- Sufficient yield in 81%
- 17 (65%) with M3
- 5 (15%) metastatic deaths

M3: No correlation with tumour size or location

Additional comments on quality of study
Prospective??; directly applicable population, reasonable sized study, long follow-up
Results

Applicable?
Conclusions

Additional comments on quality of study

Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death
Onken MD, Worley LA, Ehlers JP, Harbour JW, Cancer Research 64 7205 7209

Study Type
Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?
Conclusions

Additional comments on quality of study

Prediction of prognosis in patients with uveal melanoma using fluorescence in situ hybridisation
Patel KA, Edmondson ND, Talbot F, Parsons MA, Rennie IG, Sisley K, British Journal of Ophthalmology 85 1440 1444
Study Type: Case Series

Number of patients: 33 UM; Enucleation specimens; fresh frozen samples

Results:

- 16 UM with M3
- 14 deaths by study end
- No relationship between age, tumor size or location, or morphology

"Possibility also exists for missing genetic changes because of the small number of cells studied"

Cut-off ca. 30%

Applicable? Yes

Conclusions

Additional comments on quality of study

Retrospective; directly applicable population, smallish study size, long follow-up
Identification of monosomy 3 in choroidal melanoma by chromosome in situ hybridisation

Sandinha MT, Farquharson MA, Roberts F,
British Journal of Ophthalmology

Study Type: Case Series
Results

Variation of monosomy 3 status within uveal melanoma

Schoenfield L, Pettay J, Tubbs RR, Singh AD,
Archives of Pathology & Laboratory Medicine

Study Type: Case Series
Results

Applicable?
Conclusions

Additional comments on quality of study
N=105 UM Frozen samples
Used Karotyping FISH
FU: 5-55 months (median 27)
Local resection (n=25) or enucleation (n=74)
Follow-up time: 3yrs

Results:
Loss of heterozygosity (LOH) on chromosome 3
- 16 patients had died at study closure
- Significant assoc btwn M3 and:
  - Increasing LBD
  - Ciliary body involvement
  - Epithelioid cellularity

Interrelationship btwn particular prognostic parameters apparent; idea of prognostic index

Additional comments on quality of study
Retrospective study; directly applicable population, good sized study, reasonable follow-up time.
Study Type: Case Series

Number of patients: 924

Patient Characteristics
- Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

Additional comments on quality of study

Shields CL, Materin MA, Teixeira L, Mashayekhi A, Ganguly A, Shields JA, Ophthalmology

Small choroidal melanoma with chromosome 3 monosomy on fine-needle aspiration biopsy

Number of patients: 924

2007

Shields CL, Materin MA, Teixeira L, Mashayekhi A, Ganguly A, Shields JA, Ophthalmology

114 1919 1924

Study Type: Case Series

Number of patients: 924

Patient Characteristics
- Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?

Conclusions

Additional comments on quality of study
Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis.

Sisley K, Rennie IG, Parsons MA, Jacques R, Hammond DW, Bell SM, Potter AM, Rees RC, Genes, Chromosomes & Cancer 19 22 28

Results:

- Ciliary body involvement (p=0.003), monosomy 3 (p=0.0007) and gain of 8q (p=0.003) conferred significantly worse prognosis. Potential biomarkers for future trial design.

N=47 UM pts; Fresh samples

Follow-up: Median of 31 months

42 patients with OCM to assess effect of monosomy 3 and gain of chromosome 8q on survival

Conclusions

- M3 in 21 (50%) of UM
- Reduced survival correlated with CB involvement
- Cytogenetics may be of value in prognostication in UM

Additional comments on quality of study

Case series

Retrospective study; directly applicable population, fair sized study, reasonable follow-up time.

Multiplex fluorescence in situ hybridization identifies novel rearrangements of chromosomes 6, 15, and 18 in primary uveal melanoma

Sisley K, Tattersall N, Dyson M, Smith K, Mudhar HS, Rennie IG, Experimental Eye Research 83 554 559
Results

Applicable? N=24 primary UM
Conclusions Used Multiplex- FISH
FU: 5-55 months (median 27)

Results:
- 1 metastatic death- M3 P8
- Frequency of chr. 6 changes – 60%

"Alterations of chromosomes 1, 6, 8, 11, 15 and 18 can be more fully classified using M-FISH"

Additional comments on quality of study Retrospective??, directly applicable population, smallish study, reasonably long follow-up

Genomic profiling and identification of high-risk uveal melanoma by array CGH analysis of primary tumors and liver metastases

Additional comments on quality of study Diagnostic and prognostic

Tumor classification based on gene expression profiling shows that uveal melanomas with and without monosomy 3 represent two distinct entities

1556
Correlation of comparative genomic hybridization results of 100 archival uveal melanomas with patient survival

White JS, McLean IW, Becker RL, Director MA, Nath J,

Cancer Genetics & Cytogenetics

1089 [2006 Oct 1]

Addtional comments on quality of study
Correlation of cytogenetic abnormalities with the outcome of patients with uveal melanoma

White VA, Chambers JD, Courtright PD, Chang WY, Horsman DE, Cancer

Study Type: Case Series

Number of patients: Patient Characteristics/Inclusion/Exclusion

Study aim/Intervention: Comparators

Results: Outcomes recorded

Applicable? Conclusions

Additional comments on quality of study

Acquired homozygosity (isodisomy) of chromosome 3 in uveal melanoma

White VA, McNeil BK, Horsman DE, Cancer Genetics & Cytogenetics

Study Type: Case Series

Number of patients: Patient Characteristics/Inclusion/Exclusion

Study aim/Intervention: Comparators

Results: Outcomes recorded

Applicable? Conclusions

Additional comments on quality of study
Micro-RNAs associated with metastasis in uveal melanoma identified by multiplexed microarray profiling

Worley LA, Long MD, Onken MD, Harbour JW, Melanoma Research

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Diagnostic</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<td>Follow-up</td>
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2008 Jun

Results

Applicable?
Conclusions

Additional comments on quality of study
### Grading: 2+  
*Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal*

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</table>

#### Results

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

### 115  
The dynamics of serum tumor markers in predicting metastatic uveal melanoma (part 1)  
2011 Jan
Barak V, Kaiserman I, Frenkel S, Hendler K, Kalickman I, Pe'er J,  
Anticancer Research

<table>
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<tr>
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#### Results

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

### 1326  
Quantitative detection of circulating tumor cells in cutaneous and ocular melanoma and quality assessment by real-time reverse transcriptase-polymerase chain reaction  
2004 Mar 1
Keilholz U, Goldin LP, Bechrakis NE, Max N, Letsch A, Schmitt A, Scheibenbogen C, Heufelder K, Eggermont A, Thiel E,  
Clinical Cancer Research

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#### Results

**Applicable?**

**Conclusions**

**Additional comments on quality of study**
### Grading: 3 Non-analytic studies (for example, case reports, case series)

<table>
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**Proteomics of uveal melanomas suggests HSP-27 as a possible surrogate marker of chromosome 3 loss**

Coupland SE, Vorum H, Mandal N, Kalirai H, Honore B, Urbak SF, Lake SL, Dopierala J, Damato B,

Investigative Ophthalmology & Visual Science 51 12 20 2010 Jan

**Results**

---

**Immunomagnetic detection of micrometastatic cells in bone marrow in uveal melanoma patients**

Eide N, Faye RS, Hoifodt HK, Overgaard R, Jebsen P, Kvalheim G, Fodstad O,

Acta Ophthalmologica 87 830 836 2009 Nov

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Applicable?

Conclusions

Additional comments on quality of study
### Study Type
- Diagnostic

### Number of patients
- Patient Characteristics
- Study aim/Intervention

### Comparators
- Follow-up
- Outcomes recorded

### Results

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#### Applicable?
- Conclusions

#### Additional comments on quality of study

- The detection of melanoma cells in peripheral blood by reverse transcription-polymerase chain reaction

Osteopontin and 'melanoma inhibitory activity': comparison of two serological tumor markers in metastatic uveal melanoma patients


- Study Type: Diagnostic
- Number of patients
- Study aim/Intervention
- Comparators
- Follow-up
- Outcomes recorded
- Results

Tyrosinase mRNA levels in the blood of uveal melanoma patients: correlation with the number of circulating tumor cells and tumor progression


- Study Type: Case Series
- Number of patients
- Study aim/Intervention
- Comparators
- Follow-up
- Outcomes recorded
- Results

Experimental and prognostic
### Circulating tumor cells as prognostic factor for distant metastases and survival in patients with primary uveal melanoma

**Schuster R, Bechrakis NE, Stroux A, Busse A, Schmittel A, Scheibenbogen C, Thiel E, Foerster MH, Keilholz U,**

*Clinical Cancer Research*

<table>
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**Comparators**

**Follow-up**

**Outcomes recorded**

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

Prognostic

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### Detection of melanocytes from uveal melanoma in peripheral blood using the polymerase chain reaction

**Tobal K, Sherman LS, Foss AJ, Lightman SL,**

*Investigative Ophthalmology & Visual Science*

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**Comparators**

**Follow-up**

**Outcomes recorded**

**Results**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

Not true Dx study - not sens/spec
study
### Grading: 3 Non-analytic studies (for example, case reports, case series)

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### Results

502  Long-term outcomes of eye-conserving treatment with Ruthenium(106) brachytherapy for choroidal melanoma

Verschueren KM, Creutzberg CL, Schalij DN, Ketelaars M, Klijsen FL, Haeseker BI, Ligtenberg SM, Keunen JE, Marijnen CA,

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| Results |
|---------|-----------|-----------|-------------------|
|         |           |           |                   |
Q1a. What is the optimal method of staging?

Grading: 2+

Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

7456 Preoperative staging of liver metastases from uveal melanoma by magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET) 2010 Feb
Servois V, Mariani P, Malhaire C, Petras S, Piperno NS, Plancher C, Levy GC, Lumbroso LR, Desjardins L, Salmon RJ,

European Journal of Surgical Oncology 36 189 194

Study Type: Case-Control

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Number of patients

Inclusion/Exclusion

Results

A staging study prior to liver resection

Pts with suspected liver mets on USS/CT underwent MRI and FDG-PET preop (1-31d prior). Intraop findings + intraop USS compared to PET + MR.

Reported (MRI by 2 clinicans, PET by 1 clinician) without knowledge of the other mode’s result but knowing liver mets suspected on USS/CT.

12 of 15 pts underwent resection, 28 lesions resected, 9 were <5mm in 1 pt, 4 lesions showed up on MR not on PET, 3 other lesions in 3 pts similarly on MR not on PET

1 FP for MR, 0 for PET

PPV: MR 98%, PET 100%

Sensitivity for lesions >5mm: 100% for MR, 61% for PET

All lesions not detected by MR were capsular 1-2mm lesions

PET did not identify 2 >10mm lesions, and 5 intraparenchymal nodules 5-10mm

Suggest MRI is better, and appears to sometimes suggest miliary (inoperable) disease (though no data for this)

Additional comments on quality of study

Grading: 3

Non-analytic studies (for example, case reports, case series)

7474 Whole body PET/CT for initial staging of choroidal melanoma 2005 Oct
52 patients with choroidal melanoma underwent whole body PET/CT as part of their metastatic investigation. PET/CT scans were used as a screening tool at the time of their initial diagnosis. The standards for reference were further imaging and/or subsequent biopsies. Two of 52 (3.8%) patients were found to have metastatic melanoma before treatment. The most common sites for metastases were the liver (100%). PET/CT showed false positive results in three patients (5.7%) when further evaluated by histopathology and/or additional imaging.

Additional comments on quality of study

Demonstrates usefulness of PET in staging suspected metastatic disease. No comparator
Used subsequent imaging or biopsy to confirm whether PET correct
## 18F-fluorodeoxyglucose positron emission tomography/computed tomography and magnetic resonance imaging in patients with liver metastases from uveal melanoma: Results from a pilot study


**Study Type** - Diagnostic

**Number of patients** - 10 patients with histologically confirmed liver metastases participating in a phase III trial selecting for liver metastases only. The prevalence not stated

**Study aim/Intervention** - PET CT versus contrast liver MRI. Both are relevant to the question of optimal imaging

**Comparators** - No gold standard in uveal melanoma but contrast MRI is the gold standard in liver malignancy.

**Patient Characteristics**

- Inclusion/Exclusion
- **Results**
  - MRI detected more lesions especially when lesion size <1.2 cm. MRI detected 96% of lesions. PET identified 35% 79% of MRI lesions >1.2 cm were identified on PET 11% of MRI lesions <1.2 cm were identified on PET Specificity not stated

**Applicable?** - Yes, stage 4 disease but only confined to liver

**Conclusions**

- The study is small but provides some preliminary data on alterations in SUV in metastases that are responding to treatment versus those that are progressing.
- MR superior to PET for lesion detection below 12 mm.

**Additional comments on quality of study**

- Yes, stage 4 disease but only confined to liver

## Limited value of 18F-FDG PET/CT and S-100B tumour marker in the detection of liver metastases from uveal melanoma compared to liver metastases from cutaneous melanoma

**Strobel K, Bode B, Dummer R, Veit HP, Fischer DR, Imhof L, Goldinger S, Steinert HC, von Schulthess GK,**

**Study Type** - Case Series

**Number of patients** - Yes, stage 4 disease but only confined to liver

**Patient Characteristics**

- Inclusion/Exclusion

**Study aim/Intervention** - Who conducted the study and what was the aim of the research?

**Comparators** - Limited value of 18F-FDG PET/CT and S-100B tumour marker in the detection of liver metastases from uveal melanoma compared to liver metastases from cutaneous melanoma

**Follow-up** - 2009 Nov

**Outcomes recorded**

- 36 1774 1782
Applicable?  Partly

Conclusions

Retrospective, single centre

Looked at 13pts with proven liver mets, and correlate with FDG PET/CT imaging

Total 27mets, 50% FDG negative
4pts had extrahepatic mets (lung, bone, LN, peritoneal) - all FDG +ve (all had FDG+ve liver mets)

Serum S-100B taken in 6 pts, 4 were normal, 2 were raised

Concluded PET not sensitive enough for detecting UM liver mets

Additional comments on quality of study
### Q5. What is the optimal management of liver only metastases?

#### Grading: 1++  
*High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias*

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<th>Number of patients</th>
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<tr>
<td>9137</td>
<td>Randomized phase III trial of intravenous (IV) versus hepatic intra-arterial (HIA) fotemustine in patients with liver metastases from uveal melanoma: Final results of the EORTC 18021 study</td>
<td>171</td>
<td>First line UM</td>
<td>Ia</td>
<td>iv chemo</td>
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<td>8794</td>
<td>Percutaneous hepatic perfusion (PHP or ChemoSat) with melphalan versus best alternative care (BAC) in patients (pts) with hepatic metastases from melanoma: A post hoc analysis of PHP-randomized versus BAC-to-PHP crossover versus BAC-only pts</td>
<td>8794</td>
<td>First line UM</td>
<td>Ia</td>
<td>iv chemo</td>
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**Results**
- NO OS gain. Improved RR, PFS

**Applicable?** Yes, RCT with no OS

**Conclusions**
- Good
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
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<td>Number of patients</td>
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<td>93 pts in study. 28 crossed over from BAC to PHP</td>
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<td>Follow-up</td>
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<td>Outcomes recorded</td>
<td>Efficacy of intervention and toxicity</td>
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<tr>
<td>Results</td>
<td>11 month MS</td>
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Applicable? | Supports concept for liver targeted treatment |

Conclusions |  |

Additional comments on quality of study | Good |

8935 Chemosaturation therapy with percutaneous hepatic perfusions of melphalan versus standard of care in patients with hepatic metastases from melanoma: A randomized multicenter phase 3 study

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Applicable? | Yes, RCT Phase III with no OS gain |

Conclusions |  |

Additional comments on quality of study | Good - |
Isolated hypoxic hepatic perfusion with orthograde or retrograde flow in patients with irresectable liver metastases using percutaneous balloon catheter techniques: a phase I and II study

van EB, Brunstein F, van Ilken MG, Marinelli AW, Verhoef C, van dS, Guetens G, de BG, de Bruijn EA, de Wilt JH, Eggermont AM,

Annals of Surgical Oncology

2004 Jun

11 598 605

Applicable? Conclusions

This is a report of 2 methods of performing isolated hypoxic hepatic perfusion. 18 patients are included although only one had OM liver metastases. The orthograde technique had an associated leak rate of 56%, retrograde 36%, resulting in significant systemic toxicity. The authors abandoned the procedure.

Additional comments on quality of study

Phase I/II randomized trial of intrahepatic arterial infusion chemotherapy with cisplatin and chemoembolization with cisplatin and polyvinyl sponge in patients with ocular melanoma metastatic to the liver

Agarwala SS, Panikkar R, Kirkwood JM,

Melanoma Research

2004

14 217 222

Applicable? Conclusions

This is a report of 2 methods of performing isolated hypoxic hepatic perfusion. 18 patients are included although only one had OM liver metastases. The orthograde technique had an associated leak rate of 56%, retrograde 36%, resulting in significant systemic toxicity. The authors abandoned the procedure.

Additional comments on quality of study
mg/m² 6 Cisplatin
125 mg/m²+PVS 6

Results
Outcomes: toxicity, survivals  Effect size: none given

Applicable? No, this is uncontrolled, single centre and retrospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial

Conclusions phase I/II trial of regional liver therapy in UM patients. No control arm. Toxicity and feasibility only

Applicable? No

Conclusions

Additional comments on quality of study
uncontrolled, single centre and retrospective phase I/II trial

9338  Radioembolization for treatment of metastatic ocular melanoma to the liver: An initial experience 2011

Study Type Cohort
Number of patients 4/144
Patient Characteristics Mixed
Inclusion/Exclusion
Study aim/Intervention Radioembolisation
Comparators
Follow-up OS
Outcomes recorded OS

Results 12.5mths OS

Applicable? No

Conclusions

Additional comments on quality of study Poor

9329  Isolated Hepatic Perfusion (IHP) for patients with unresectable liver metastases 2011
### Study Type
- **Cohort**

### Number of patients
- **Patient Characteristics**
- **Inclusion/Exclusion**

### Study aim/Intervention

### Comparators

### Follow-up

### Outcomes recorded

### Results

#### Applicable?

#### Conclusions

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**Grading:** 3  
**Non-analytic studies (for example, case reports, case series)**

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<th>Case Series</th>
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| **1415**         | Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver | 29pts              | Inclusion/Exclusion     | Regional therapy of MUM: IHP |             | 10% CR, 52% PR, PFS | 8mths, OS 12mths.  
|                  |                              |                    |                         |                          |             | Prognostic factors for OS on univariate LDH, Number of mets, size of largest met, % liver replacement. LDH only factor on multivariate |
Survival of patients with primary and non-colorectal secondary liver malignancies treated with Yttrium-90 radioembolization in a salvage situation


Study Type: Cohort
Number of patients: 29 (2 UM)
Patient Characteristics: Liver mets
Study aim/Intervention: Radioembolisation
Comparators: none
Follow-up: til death
Outcomes recorded: OS
Results: Not stated

Intra-arterial hepatic carboplatin-based chemotherapy for ocular melanoma metastatic to the liver. Report of a phase II study


Study Type: Case Series
Number of patients: 8978
Patient Characteristics: 29 (2 UM)
Study aim/Intervention: Radioembolisation
Comparators: none
Follow-up: til death
Outcomes recorded: OS
Results: Not stated

Applicable? No
Conclusions
Additional comments on quality of study: Poor
N = 8 OM with liver metastases
Tx = IA hepatic carboplatin-based chemotherapy (300 mg/m² once every two wks) at an out-patient clinic.
All pts had laparotomy with surgical implantation of an arterial port device through the gastroduodenal artery.

RESULTS:
- Overall response rate = 38% with median survival time of 15 months.
- Regimen was well tolerated: main toxicity was myelosuppression.

AUTHORS' CONCLUSIONS: Carboplatin seems suitable for intra-arterial hepatic chemotherapy and active in ocular melanoma metastatic to the liver

Additional comments on quality of study
Direct/applicable population; Small study (but rare condition)

7438 Outcome of patients following hepatic resection for metastatic cutaneous and ocular melanoma 2011 Mar
Journal of Hepato-biliary-pancreatic Sciences 18 268 275

Study type: Case Series

Number of patients
Patient characteristics
Study aim/intervention
Comparators
Follow-up
Outcomes recorded

Results

No

14 patients with liver only disease (6 ocular primary, 8 skin). Some received chemo post surgery. All received chemo on liver recurrence.
The median overall survival was 26.3 months (range 0.5–103.5 months). Actuarial 1- and 3-year survival rates in the whole cohort were 77 and 49%, respectively. The cause of death was disease progression in all patients.

Additional comments on quality of study
This is a case series review of 7 patients with OM hepatic metastases treated with intra-arterial fotomustine. 10 patients were considered for treatment, 1 was excluded for impaired liver function, and 2 for failure of port implantation. 7 patients were recruited.

A portcath was inserted into the CHA via the GDA. Fotomustine was delivered at 100mg/m2 over 4 hours weekly for 4 weeks, before a 5 week rest period and then maintenance therapy (3 weekly until progression or death).

2 patients had PR, 2 had stable disease, and 2 progressed. Toxicity was low, median survival 24 months (range 4 to 50+ months).

This study, although limited in size and design, suggests a benefit of treatment with intra arterial fotomustine.

Additional comments on quality of study

No, this is uncontrolled, single centre and retrospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial

Median time to progression was 6.2 months (95% CI 3.7-10.5) and median overall survival was 21 months (95% CI 8-39)
Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study


**Study Type**: Case Series
**Number of patients**: 10 pts,

**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

Median f/u was ~6 months

- All had LM and chemo +/-immunotherapy +/- intra-arterial fotemustine
- 5 had 1 cycle of irinotecan TACE, 5 had 2 cycles. Criteria for undergoing 2 cycles not stated
- All pts had reduction in disease, better % response in those with low volume disease.
- 3 had 90% reduction, 3 had 80%, and 4 had 60 - 79% reduction.
- SE: ileus, 2 had non-icteric hepatitis
- 80% pts reported improvement in QoL

**Additional comments on quality of study**

- single centre, prospective, phase 2 study, 10 pts, no randomisation. Median f/u was ~6 months

---

Long-term survival of uveal melanoma patients after surgery for liver metastases


**Study Type**: Case Series
**Number of patients**: 23

**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

- 131
- 137

---

**Additional comments on quality of study**

- single centre, prospective, phase 2 study, no randomisation.
Results

**Applicable?** Partly

- Single centre, case series, retrospective, over 20 years, non-randomised

74 pts with liver mets, 35 underwent resection

Resection criteria:
1. mets confined to liver
2. imaging indicates feasible curative resection
3. no prohibiting comorbidities

Reports matched in terms of age, primary tumour size. No mention of matching comorbidity, total tumour load. No report of how many eligible for surgery declined. Therefore likely significant selection bias.

Intraarterial chemo used for some resected pts + immunotherapy but no details and not analysed separately. No report of systemic treatments for non-resected pts.

Results: median metastatic survival (months):
- non-operated - 6.8
- operated - 23
- R0 - 65.6
- R1/2 - 16.6
(p-value > 0.05)

Survival also correlates with number of mets (though tumour load not reported), and number of mets correlates with probability of achieving R0 resection.

**Additional comments on quality of study**

<table>
<thead>
<tr>
<th>7444</th>
<th>Radioembolization as salvage therapy for hepatic metastasis of uveal melanoma: a single-institution experience</th>
<th>2011 Feb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonsalves CF, Eschelman DJ, Sullivan KL, Anne PR, Doyle L, Sato T,</td>
<td>AJR 196 468 473</td>
<td></td>
</tr>
</tbody>
</table>

**Study Type**
- Case Series

**Number of patients**
- 32

**Patient Characteristics**
- Pretreated UM

**Study aim/Intervention**
- second line regional therapy

**Comparators**
- no controls

**Follow-up**
- Tumour burden < 25% and response stat significant for PFS

**Outcomes recorded**
Applicable? no

Conclusions

single institution case series of second line regional therapy with no controls. Tumour burden <25% and response stat significant for PFS

Additional comments on quality of study

Poor-single institution case series

7452

Hepatic artery chemoembolization in patients with ocular melanoma metastatic to the liver: response, survival, and prognostic factors


Study Type

Case Series

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>Male</td>
<td>68</td>
<td>54</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>No</td>
<td>82</td>
<td>66</td>
</tr>
<tr>
<td>Extent of liver involvement (N 113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>25%–50%</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>50%–75%</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>75%</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Extrahepatic disease at time of HACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>78</td>
<td>62</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td>60 (18–87)</td>
<td></td>
</tr>
<tr>
<td>Mean no. HACE sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(range)</td>
<td>2 (1–8)</td>
<td></td>
</tr>
</tbody>
</table>

Comparators

TACE

systemic chemo

Follow-up

Outcomes recorded
No, this is uncontrolled, single centre and retrospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial single centre retrospective case series evaluating multiple agents delivered via intrahepatic route. Extent of liver involvement (>75%), LDH and response identified as prognostic factors for OS on multivariate analysis.

Additional comments on quality of study

yes

Study Type

Case Series

Results

Selected patients with metastatic melanoma may benefit from liver resection 2007


Number of patients

848

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Applicable? Conclusions

yes

18 suitable patients based on imaging and other criteria: absence of extra-hepatic disease after evaluation with CT/MRI and FDG-PET scans; disease-free interval longer than 24 months after the resection of the primary melanoma; presumed completely resectable lesions; absence of clinical co-morbidities.

10 resected (8 had 1 or 2 mets), 8 found to have diffuse liver disease or extra-hepatic disease at op. 5 ocular, 5 cutaneous.

Overall median survival was 22 months; overall survival and disease-free survival were 70% and 50% respectively.

Very select group

Additional comments on quality of study

Prolonged survival after complete resection of metastases from intraocular melanoma 2004 Jan 1

This study presents a retrospective case series review of a single centre experience in treating patients with metastatic OM. Between 1971 and 1999, 112 patients were identified. 70% had liver disease at diagnosis, with 70% of these having more than 5 lesions. 24/112 patients underwent surgical resection of liver metastases, with complete resection in 21 (88%). 17 surgical patients received some form of adjuvant treatment, the remainder were followed. The sample size was too small to investigate the effect of adjuvant treatment. For pts with hepatic mets, median survival and 5 year survival were 9 months and 2%, compared to 28 months and 22% for those without liver mets. With surgery, this improved to 38 months and 39 months. The only significant prognostic variable for survival on multivariate analysis was surgical resection, confirmed in a subset propensity analysis.

This study provides useful data supporting the role of surgical resection in selected cases of ocular melanoma liver metastases.

### Additional comments on quality of study

7453 Transarterial chemoembolization of liver metastases in patients with uveal melanoma 2010 Jun
Huppert PE, Fierlbeck G, Pereira P, Schanz S, Duda SH, Wietholtz H, Rozeik C, Claussen CD,
European Journal of Radiology 74 e38 e44

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Male 8, Female 6</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>Age 36–77 (mean 61.4) years, Number of metastases 2–4, 7–9, &gt;20, Size of metastases 1–12 (mean 7.1) cm, Liver volume occupied by tumor &lt;25%</td>
</tr>
<tr>
<td>Study aim/Intervention</td>
<td>TACE</td>
</tr>
<tr>
<td>Comparators</td>
<td>Historical systemic chemo</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Outcomes recorded</td>
<td></td>
</tr>
</tbody>
</table>
No, this is uncontrolled, single centre and prospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial.

Applicable? No, this is uncontrolled, single centre and prospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial.

Conclusions single centre series 14pts. Outcomes correlated with tumour burden (<25%)

Additional comments on quality of study

4761 A first report of radioembolization for hepatic metastases from ocular melanoma 2009 Jul


Study Type Case Series

Number of patients Patient Characteristics Inclusion/Exclusion

Study aim/Intervention Yttritium 90 radioablation Variable whole liver treatment, or sequential lobar depending on centre

Comparators

Follow-up 1 year

Outcomes recorded N/A

Results 1 CR, 6 PR, 1 SD, 1 PD at 3 months

Applicable? multicentre (S) retrospective

Conclusions Yttritium 90 radioablation

Variable whole liver treatment, or sequential lobar depending on centre

all had bilobar disease >4 mets

8 had whole liver treatment, 3 to R lobe only

1 CR, 6 PR, 1 SD, 1 PD at 3 months

80% survival at 1 year
Low toxicity. 1 Grade 3 toxicity (GU)

Additional comments on quality of study  multicentre (5) retrospective

9114 Radioembolization for treatment of metastatic ocular melanoma to the liver: An initial experience 2011

Study Type  Case Series
Number of patients
Patient Characteristics  Study aim/Intervention
Inclusion/Exclusion
Comparators
Follow-up
Outcomes recorded

Applicable?  Yes

N=144 pts with OM and liver metastases BUT ONLY N=4 underwent Tx with liver-directed radioembolization (LR)

- Median interval from Dx of OM to MOML = 5.4 yrs
- Median time from MOML to first LR = 5.5 months (33 days from first LR consult to first LR).
- Median of 61% of recommended dose was deliverable.
- LR was done to both lobes of the liver in one session.
- Median follow up = 18.4 months.

RESULTS:
- No major complications.
- Grade-1 toxicity occurred after 53% of treatments and resolved within the first 48 hrs.
- Intrahepatic disease burden improved after 73% of LRs
- Extrahepatic disease worsened after 45% of LRs.
- Median survival from Dx of MOML = 18.4 months
- Median survival from time of first LR = 12.5 months.
- No correlation between survival and how early LR was done (from time of Dx of MOML (p = 0.21).

Conclusion: LR treatment is safe in management of pts with MOML and can result in intrahepatic improvement of disease burden.

CONFERENCE ABSTRACT (not full paper)

Additional comments on quality of study  Small pt number (N=4); direct/applicable population; conference abstract

9140 Isolated Hepatic Perfusion (IHP) for metastases of ocular malignant melanoma 2012
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Study aim/Intervention</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>IHP</td>
</tr>
<tr>
<td>Comparators</td>
<td>None</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Til death</td>
</tr>
<tr>
<td>Outcomes recorded</td>
<td>RR, OS</td>
</tr>
<tr>
<td>Results</td>
<td>Median OS 27 months</td>
</tr>
<tr>
<td>Applicable?</td>
<td>Yes</td>
</tr>
<tr>
<td>Conclusions</td>
<td></td>
</tr>
</tbody>
</table>

**Additional comments on quality of study**
Moderate

---

**Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie**

Mariani P, Piperno NS, Servois V, Berry MG, Dorval T, Plancher C, Couturier J, Levy, European Journal of Surgical Oncology, 2009 Nov

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Study aim/Intervention</td>
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<tr>
<td>Inclusion/Exclusion</td>
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<tr>
<td>Comparators</td>
<td></td>
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<tr>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Outcomes recorded</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>Applicable?</td>
<td>Partly</td>
</tr>
</tbody>
</table>
| Conclusions      | Retrospective, single centre, large numbers

**Comparables** 543 pts with liver mets treated with systemic chemo (dacarbazine/fotemustine/phase 1/2 trials/supportive care) with 255 who underwent resection (microscopically complete/incomplete/macroscopically incomplete)

Macro incompletes had intra hepatic artery dacarbazine/fotemustine

Median survival 14 months (resection) vs 8 months (no resection)
However likely selection bias

With multivariate analysis, four variables were found to independently correlate with prolonged survival: an interval from primary tumour diagnosis to liver metastases >24 months, comprehensiveness of surgical resection (R0), number of metastases resected (< or = 4) and absence of miliary disease

No details on chemo cycles, which 8 had RFA etc

Additional comments on quality of study

Liver metastases from uveal melanoma: clinical experience of hepatic arterial infusion of cisplatin, vinblastine and dacarbazine


597 10 patients

Study Type Case Series
Number of patients
Patient Characteristics Inclusion/Exclusion
Study aim/Intervention hepatic arterial infusion cisplatin , vinblastine and dacarbazine
Comparators
Follow-up
Outcomes recorded

Results
2 had an objective response, 4 patients had stable disease and 4 patients had progressive disease.

Median survival from the start of therapy was 16 (range 5 - 69) months.

HAI of second line agents was of limited effectiveness.

Applicable?

All patients with progressive disease died within one year while all patients with clinical benefit response (objective response or stable disease) survived more than one year.

Conclusions

retrospective

Liver metastases from uveal melanoma: clinical experience of hepatic arterial infusion of cisplatin, vinblastine and dacarbazine


7464 10 patients

Study Type Case Series
Number of patients
Patient Characteristics Inclusion/Exclusion
Study aim/Intervention hepatic arterial infusion cisplatin , vinblastine and dacarbazine
Comparators
Follow-up
Outcomes recorded
Results

Applicable? UNABLE TO OBTAIN PAPER

Conclusions

retrospective

10 patients with hepatic mets treated with hepatic arterial infusion cisplatin, vinblastine and dacarbazine

2 had an objective response, 4 patients had stable disease and 4 patients had progressive disease.

median survival from the start of therapy was 16 (range 5 - 69) months.

HAI of second line agents was of limited effectiveness.

All patients with progressive disease died within one year while all patients with clinical benefit response (objective response or stable disease) survived more than one year.

Additional comments on quality of study

9330 Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study


Study Type Case Series

Number of patients Series of 30pts.

Twenty-four patients completed at least one treatment to all targeted liver metastases

Patient Characteristics Inclusion/Exclusion

Study aim/Intervention Regional therapy in liver mets:

Comparators

Follow-up Outcomes recorded

The overall response rates (complete and partial responses) for intention-to-treat patients and for patients who were evaluable for response were 16.7 and 20.4%, respectively

Results

OS correlated with tumour volume and response. RR 16.7%, OS 5mths

The median overall survival of the entire intention-to-treat group of patients was 5.2 months (range, 0.1-27.6 months), for patients with complete or partial response in hepatic metastases 21.9 months (range, 7.4-27.6 months), for patients with stable disease 8.7 months (range, 2.9-14.4 months) and for patients with progressive disease 3.3 months (range, 1.6-5.6 months)

13 of the 18 patients who achieved complete response, partial response or stable disease subsequently developed progression of extrahepatic metastases with control of hepatic metastases
Applicable?

Conclusions

Additional comments on quality of study

7449  Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease

Pawlik TM, Zorzi D, Abdalla EK, Clary BM, Gershenwald JE, Ross MI, Aloia TA, Curley SA, Camacho LH, Capussotti L, Elias D, Vauthey JN,

Annals of Surgical Oncology

13  712  720

Study Type  Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable?  No, this is uncontrolled, 4 centres and retrospective. This study provides preliminary support for the concept that surgery associated with improved PFS and OS than reported systemic trials (not comparable) This requires a controlled trial

retrospective case series of liver resection with median OS 29.4mths and PFS 8.8mths. 2 and 5 year OS 61.5 and 20%, respectively. Apparent consistency across surgical trials

Additional comments on quality of study

7450  Intra-arterial hepatic fotemustine for the treatment of liver metastases from uveal melanoma: experience in 101 patients


Annals of Oncology

17  578  583

Study Type  Case Series

Number of patients

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Effect of intra-arterial fotemustine on survival

Best supportive care historically
Applicable? No, this is uncontrolled, multi centre and retrospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial.

Conclusions

Additional comments on quality of study
uncontrolled, single centre and retrospective

Results

Sato T, Eschelman DJ, Gonsalves CF, Terai M, Chervoneva I, McCue PA, Shields JA, Shields CL, Yamamoto A, Berd D, Mastrangelo MJ, Sullivan KL,

Journal of Clinical Oncology 26 5436 5442

2008 Nov 20

Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor

Study Type: Case Series

Number of patients

Patient Characteristics

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable? No.

Conclusions

Phase I, single centre, unrandomised, no comparator

34 of 39 pts had UM

MTD not reached. Minimal SE, some grade 3-4 LFT derangement

Survival was 2y outcome, increased with higher doses
The median overall survival of intent-to-treat patients who had metastatic uveal melanoma was 14.4 months.

### Additional comments on quality of study

<table>
<thead>
<tr>
<th>Transarterial chemoembolization of liver metastases from uveal melanoma after failure of systemic therapy: toxicity and outcome</th>
</tr>
</thead>
</table>

#### Study Type

- **Case Series**

#### Number of patients

<table>
<thead>
<tr>
<th>n</th>
<th>Number of patients</th>
<th>25</th>
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</thead>
</table>

#### Patient Characteristics

<table>
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<table>
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</table>

<table>
<thead>
<tr>
<th>Karnofsky performance status (%)</th>
<th>90</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;90</td>
<td>4</td>
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</tbody>
</table>

#### Prior systemic therapy

- 25 Chemotherapy
- 22 Immunotherapy
- 6 Vaccine
- 2 Vaccine

#### One prior line

<table>
<thead>
<tr>
<th>Median (range) (months)</th>
<th>9 (2–24)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pretreatment LDH &gt; Two-fold ULN</th>
<th>11</th>
</tr>
</thead>
</table>

#### Time between diagnosis of metastases and TACE

<table>
<thead>
<tr>
<th>Cytostatic drug used for TACE</th>
<th>BSC AND SYSTEMIC CHEMO</th>
</tr>
</thead>
</table>
Results

Applicable? No

Conclusions
TACE after failure of systemic treatment, retrospective

n = 25, 11 had extrahepatic mets (lung, skin, bone, kidney)

variety of prior systemic chemo/immunotherapy

16 had fotemustine TACE, 9 had systemic fotemustine before so had cisplatin TACE
Either complete liver perfusion/lobar/sequential/to single met

Response evaluated by 2 experienced radiologist with a 3rd if disagreement

No reported grade 4 toxicity, 6 events of grade 3

PR and SD at 2 months in 14 pts (2-9 months)
No significant difference between cisplatin + fotemustine group
2 had extrahepatic progression

1yr survival 15%

Survival longer if pre-treatment LDH was low.

Additional comments on quality of study yes

7468 Hepatic arterial chemoembolization for management of metastatic melanoma 2008 Jan

Study Type Case Series
Number of patients Patient Characteristics Study aim/Intervention
Inclusion/Exclusion
Comparators Follow-up Outcomes recorded

Results
Single centre, unrandomised, no comparator

20 pts includes 17 ocular (uveal/conj?) and 3 cutaneous

Chemoembolization with cisplatin, doxorubicin and mitomycin C, some multiple treatments

Results not separated by disease. None had partial/complete responses.
65% stable, 35% progressed at 4-6 weeks.

The mean and median overall survival times were 334 +/- 71 and 271 days

Postulates tumour response relates to nodular or infiltrative angiographic appearance as these relates to survival. Nodular median survival >2yrs, infiltrative 115 days.

Additional comments on quality of study

927 Hepatic arterial Fotemustine chemotherapy in patients with liver metastases from cutaneous melanoma is as effective as in ocular melanoma

Study Type Case Series
Number of patients
Patient Characteristics Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results

Applicable? Yes
Conclusions

A retrospective non-comparitive case series. Ocular and cutaneous melanoma pts are included (18 Omel). Median survival is 22months with OM and 9 months with CM (non significant). As they make no comparison to other treatments, this study is of little help in answering the key questions.

Additional comments on quality of study

9269 Chemosaturation therapy with percutaneous hepatic perfusion (CS-PHP) for unresectable hepatic metastases-the european institute of oncology (EIO) experience

2012
### Study Type
- Case Series

### Number of patients
- 4 (3 OCM)

### Patient Characteristics
- Liver mets

### Study aim/Intervention
- IHP

### Comparators
- None

### Follow-up
- Efficacy of intervention and toxicity

### Outcomes recorded

### Results
- No grade 4 toxicity
- Mean operation time 4 hrs
- PR in 3, SD in 3, DP in 2

### Applicable?
- No

### Conclusions
- No consecutive, single centre
- None had previous chemo
- 8 pts OM
- 1 had wound infection, none had chemical cholecystitis/bile duct necrosis
- No grade 4 toxicity

---

### Study Type
- Case Series

### Number of patients
- 8 pts OM

### Patient Characteristics
- Liver mets

### Study aim/Intervention
- Isolated hypoxic hepatic perfusion with melphalan in patients with irresectable ocular melanoma metastases

### Comparators
- None

### Follow-up
- 2009 May

### Outcomes recorded

### Results
- No grade 4 toxicity
- Mean operation time 4 hrs
- PR in 3, SD in 3, DP in 2

### Applicable?
- No

### Conclusions
- No consecutive, single centre
- None had previous chemo
- 8 pts OM
- 1 had wound infection, none had chemical cholecystitis/bile duct necrosis
- No grade 4 toxicity
Mean operation time 4 hrs

PR in 3, SD in 3, DP in 2

Median time to local progression was 6 months and the median survival was 11 months

Additional comments on quality of study

consecutive, single centre

802 Isolated hepatic perfusion with 200 mg melphalan for advanced noncolorectal liver metastases

van Iersel LB, Hoekman EJ, Gelderblom H, Vahrmeijer AL, van Persijn van Meerten EL, Tijl FG, Hartgrink HH, Kuppen PJ, Nortier JW, Tollenaar RA, van d,

Annals of Surgical Oncology

2008 Jul

15 1891 1898

Study Type Case Series

Number of patients

13 of 19 pts in study had UM, others had other primaries

Study aim/Intervention

Laparotomy + prophylactic cholecystectomy, mean 8hrs op time, mean 3.5L blood loss, 10/19 serious hepatic toxicity, 5 VTE

5% underwent laparotomy but abandoned due to extrahepatic disease not seen on CT

Results

UM pts: 33% PR, 50% SD, 17%DP

All progressed in f/u, unclear time period

Applicable? No.

Conclusions

Single centre, unrandomised, no comparator

Additional comments on quality of study

Single centre, unrandomised, no comparator

9279 TACE with irinotecan-preloaded DC bead in uveal melanoma liver metastases: Efficacy, predictive value of DSA/DW-MRI


2012

Study Type Case Series

Number of patients

10

Study aim/Intervention

DEBIRI

Comparators

pre-treated >5 mets vs untreated <5 mets

Follow-up

Radiological response

Outcomes recorded
### Results

1CR, 3PR, 4SD, 2PD (second-line DEBIRI: 1PR, 3SD, 1PD; first-line DEBIRI: 1CR, 2PR, 1SD, 1PD)

---

### Applicable?

Suggests less response in hypovascular infiltrative lesions.

### Conclusions

#### Additional comments on quality of study

Poor

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7472

Preliminary experience with transarterial chemoembolization (TACE) in liver metastases of uveal malignant melanoma: local tumor control and survival


### Study Type

Case Series

### Number of patients

12 pts with liver metastases from UM

### Patient Characteristics

Inclusion/Exclusion

### Study aim/ Intervention

TACE with mitomycin C, mean 4.7 cycles

### Comparators


### Follow-up


### Outcomes recorded


### Results

Better response in pts with hypervascular mets (6, either stable or regressed)

Progression only in the moderate (5)/ hypovasc (1).

3 had disease regression - 19.6 months mean survival

5 had stable disease - 21.3

4 progressed - 8.3

Minimal SE. No reported complications.

---

### Applicable?

This is a case series, reporting results of conventional TACE with cisplatin/lipiodol in patients with up to 6 metastases

Three patients responded to TACE with a size reduction of more than 50% (partial response), five patients with stable disease, and four patients with progressive disease with an increase in volume of more than 25%.

Mean survival following primary tumor treatment was 32.9 months, and after first embolization 19.5 months.

Single centre, unrandomised, no comparator

12 pts with liver metastases from UM

All had different previous treatment (8 systemic chemo/ 4 surgical resection /3 RTx)

TACE with mitomycin C, mean 4.7 cycles

Better response in pts with hypervascular mets (6, either stable or regressed)

Progression only in the moderate (5)/hypovasc (1).
3 had disease regression - 19.6 months mean survival
5 had stable disease - 21.3
4 progressed - 8.3

Minimal SE. No reported complications.

Additional comments on quality of study

Single centre, unrandomised, no comparator

7448 High-dose immunoembolization: survival benefit in patients with hepatic metastases from uveal melanoma
Yamamoto A, Chervoneva I, Sullivan KL, Eschelman DJ, Gonsalves CF, Mastrangelo MJ, Berd D, Shields JA, Shields CL, Terai M, Sato T,

Study Type Case Series
Number of patients
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Applicable? No, this is uncontrolled, single centre and retrospective. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials. This requires a controlled trial

Conclusions

retrospective review of prognostic factors in UM patients undergoing regional therapies. Hypothesis generating only. Multivariate analysis identified response, female and age < 60yrs

Same patient group as in RID 7467

Additional comments on quality of study

uncontrolled, single centre and retrospective.

8930 Resection of liver metastases from ocular melanoma remains discussional: An experience with 5 cases
Yang X, Yang J, Lu K, Zhang Y, Zhang B, Shen F, Wu M,

Academic Journal of Second Military Medical University 33 1035 1037
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<tr>
<td>Patient Characteristics</td>
<td>Liver mets</td>
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<tr>
<td>Inclusion/Exclusion</td>
<td></td>
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<tr>
<td>Study aim/Intervention</td>
<td>surgery and TACE</td>
</tr>
<tr>
<td>Comparators</td>
<td>None</td>
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<tr>
<td>Follow-up</td>
<td>til death</td>
</tr>
<tr>
<td>Outcomes recorded</td>
<td>OS post op</td>
</tr>
<tr>
<td>Results</td>
<td>MOS 9.6 months</td>
</tr>
<tr>
<td>Applicable?</td>
<td>No</td>
</tr>
<tr>
<td>Conclusions</td>
<td></td>
</tr>
<tr>
<td>Additional comments on quality of study</td>
<td>Poor</td>
</tr>
</tbody>
</table>
**Q2a. Is there a preferred prognostic method for a patient with metastatic disease?**

**Grading:** 2+  
Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
</tr>
</thead>
</table>

Study Type: Cohort  

**Grading:** 3  
Non-analytic studies (for example, case reports, case series)

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<thead>
<tr>
<th>Number of patients</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
</tr>
</thead>
</table>

Results

Applicable? No  

Conclusions

Looked at alterations in genetic expression before and after hepatic perfusion of melphalan. Endpoint not survival/tumour reduction  

Additional comments on quality of study
Results

Results: median metastatic survival (months):
non-operated - 6.8
operated - 23
R0 - 65.6
R1/2 - 16.6
(p-value >0.05)

Applicable? Partly
Conclusions Survival also correlates with number of mets (though tumour load not reported), and number of mets correlates with probability of achieving R0 resection.

Additional comments on quality of study
Single centre, caseseries, retrospective, non-randomised over 20 years,

Study Type Case Series
Number of patients
Study aim/Intervention case series evaluating multiple agents delivered via intrahepatic route.
Comparators Extent of liver involvement (>75%), LDH and response identified as prognostic factors for OS on multivariate analysis
Follow-up
Outcomes recorded

Applicable? No. This study provides preliminary support for the concept that regional therapy produces a higher response rate and PFS than reported systemic trials,. This requires a controlled trial

Additional comments on quality of study this is uncontrolled, single centre and retrospective.

428 Transarterial chemoembolization of liver metastases in patients with uveal melanoma 2010 Jun
Results

Looking at prognostic features in patients found to have liver mets on surveillance.

63 (10.5%) out of 602 patients developed liver metastases

55% received chemo or BSC
45% underwent surgery and chemo

The median overall survival after diagnosis of liver metastases was 15 months. It reached 25 months for selected patients with complete resection (P=0.0002)

The two independent favorable prognostic factors are fewer than ten metastases at screening and the absence of ciliary body involvement
Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor

Sato T, Eschelman DJ, Gonsalves CF, Terai M, Chervoneva I, McCue PA, Shields JA, Shields CL, Yamamoto A, Berd D, Mastrangelo MJ, Sullivan KL,

Journal of Clinical Oncology 2008 Nov 20

Additional comments on quality of study

Phase I, single centre, unrandomised, no comparator

Results

MTD not reached. Minimal SE, some grade 3-4 LFT derangement
Survival was 2y outcome, increased with higher doses

Hepatic arterial chemoembolization for management of metastatic melanoma

Sharma KV, Gould JE, Harbour JW, Linette GP, Pilgram TK, Dayani PN, Brown DB,

AJR 2008 Jan

Additional comments on quality of study

Postulates tumour response relates to nodular or infiltrative angiographic appearance as these relates to survival. Nodular median survival >2yrs, infiltrative 115 days.

Results

Results not separated by disease. None had partial/complete responses.
65% stable, 35% progressed at 4-6 weeks.
| Additional comments on quality of study | Single centre, unrandomised, no comparator |
**Grading: 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**

519 Effectiveness of treatments for metastatic uveal melanoma 2009


Study Type Systematic Review

Number of patients Phase I/II clinical trials, case series, case reports, review articles.

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Results

Applicable? UNABLE TO GET FULL PAPER TO CHECK IF LOOKED AT STUDY QUALITY, SO HAVE PUT N/A FOR THIS

Conclusions

Additional comments on quality of study

The largest reported unselected patient groups: median survival of 3 to 4 months after detection of metastasis.

The largest selected patient group: substantially longer median survival times.

CONCLUSIONS: Although median survival time after diagnosis of metastatic UM tends to be substantially longer in selected patient subgroups subjected to aggressive invasive interventions than it is in unselected groups, much if not most of this apparent difference in survival is likely to be attributable to selection bias, surveillance bias, and publication bias rather than treatment-induced alteration of expected outcome.

Published peer-reviewed articles do not provide compelling scientific evidence of any survival benefit of any method of treatment for any subgroup of patients with metastatic uveal melanoma

**Grading: 3 Non-analytic studies (for example, case reports, case series)**

2591 Regional adoptive immunotherapy with interleukin-2 and lymphokine-activated killer (LAK) cells for liver metastases 1994
Yes
- N=15 pts with unresectable progressive liver metastases of melanoma (N=7 of these pts had previously failed chemotherapy or immunotherapy). ONLY N=6 PTS WERE OM.
- IA (splenic artery+ portal vein or hepatic artery) immunotherapy with IL-2 and LAK cells.

RESULTS:
- The usual side-effects of IL-2 and LAK cells occurred without limiting liver toxicity.
- None of 6 patients with metastases from ocular melanoma responded
- One partial (7+ months) and two complete responses (36 and 26+ months) were observed in 9 patients with metastases from cutaneous melanoma.

Additional comments on quality of study
Small study; phase Ib; N=6 pts with OM; half of all N=15 pts had prev failed therapy (indirect pop?)

2302 Treatment of ocular melanoma metastatic to the liver by hepatic arterial chemotherapy 1997 Jul

Study Type Case Series
Number of patients
Patient Characteristics Study aim/Intervention Comparators Follow-up Outcomes recorded
Inclusion/Exclusion

Results

Applicable? Yes
Conclusions
- N=15 pts with unresectable progressive liver metastases of melanoma (N=7 of these pts had previously failed chemotherapy or immunotherapy). ONLY N=6 PTS WERE OM.
- IA (splenic artery+ portal vein or hepatic artery) immunotherapy with IL-2 and LAK cells.

RESULTS:
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Additional comments on quality of study
Small study; phase Ib; N=6 pts with OM; half of all N=15 pts had prev failed therapy (indirect pop?)

Pts = OM with liver metastases (N=31). Liver metastases in progression (as seen by annual radiologic screening). Not previously undergone chemotherapy and all had normal hematologic and renal function.
Tx = Chemotherapy: Hepatic IA fotemustine.

Tx regimen: laparotomy to place catheter. Fotemustine given as 100 mg/m2 as a 4-hour infusion. First once/wk four times, then after a 5-wk rest period, every 3 wks until progression or toxicity.
RESULTS: prognostic role of patient survival characteristics.
- Overall objective responses (WHO criteria) = 12/30 pts (40%; 95% CI 22% to 59%).
- Complete response = 13% (n=4), Partial response = 27% (n=8).
- Median duration of response = 11 mths; Median survival time = 14 mths; n=7 pts survived ≥2 yrs.

MULTIVARIATE ANALYSIS:
- Strongest predictor for survival = Lactate dehydrogenase (LDH)

UNIVARIATE ANALYSIS:
- adverse effect of elevated LDH level was associated with median survival time of 9 mths (compared to 18 mths when in the normal range, p=0.019).
- Strongest predictor.
- Abnormal vs. normal LDH = HR 2.80 (96% CI 1.19-6.61) magnitude of effect similar in multivariate analysis.
- Similar results with serum alkaline phosphatase concentrations (p=0.04)

TOXICITY (WHO Criteria)
- WHO grade III/IV neutropenia or thrombopenia = 6/28 pts (21%)
- WHO grade III/IV nausea/vomiting = 13/28 pts (49%)
- No cases of infection or bleeding.
- Toxicity most pronounced in liver: gamma-Glutamyltransferase elevated ≥5 times normal level in N=13 pts (48%).

CONCLUSION: OA chemotherapy with fotemustine produced a high response rate and survival similar to chemoembolization therapy. It involves no major toxicity and preserves the quality of life.

To assess further its effectiveness, an RCT to compare hepatic IA vs. IV chemotherapy is being planned.

Additional comments on quality of study
Applicable/direct population; reasonable sample size (since OM is rare); methods well described; long follow-up.

2861 Phase II study of hepatic intraarterial fotemustine in patients with hepatic metastases from uveal malignant melanoma: Preliminary results
Leyvraz S, Zografos L, Bauer J, Mir A, Cour V, Pettavel J, Regional Cancer Treatment

Study Type
Case Series

Number of patients
Patient Characteristics
Inclusion/Exclusion
Study aim/Intervention
Comparators
Follow-up
Outcomes recorded

Results

Applicable? Conclusions
DATA FROM ABSTRACT ONLY AS NOT GOT FULLY PUBLISHED PAPER INTERIM RESULTS OF A STUDY

N=14 UM with hepatic metastases.
Tx = Fotemustine by IA hepatic infusion (100 mg/m<sup>2</sup>) once/wk repeated 4 times. After a 5 wk rest period, it was given every 3-4 wks till progression.

RESULTS:
- N=1 complete and N=4 partial clinical response (overall response rate 36%, 95% CI 13-65%).
- Median actuarial survival = 12 mths.
- Toxicities were minimal with WHO grade 1 median leukopenia, and grade 2 nausea and vomiting.
- Hepatic toxicity was grade 2-3 asymptomatic elevation of -GT.

Other patients will be included in the study and a longer follow-up period is needed before drawing firm conclusions.

**Additional comments on quality of study**

Direct/applicable population; small sample size (but this is only interim results); shorter follow-up than other studies (but this is only interim results)

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<th>Study Type</th>
<th>Number of patients</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
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**Results**

DATA FROM ABSTRACT ONLY AS NOT GOT FULL PAPER

has been considered a palliative therapeutic option in N=9 pts.

Tx = Liver Trans-Arterial ChemoEmbolization (TACE)
Combination of Cisplatin, Dacarbazine and Lipiodol was infused in the proper hepatic artery, and temporary embolization of the vessel was achieved using starch microspheres.

RESULTS:
- N=6 pts had regression of metastases (as seen by CT and US)
- N=2 had stable disease
- N=1 had progressive disease
- N=2 died of hepatic disease (18 and 7 mths after Dx of metastases)
- N=4 died of extrahepatic disease (after 12, 15, 20 and 27 mths)
- N=3 survived (8, 20 and 23 mths after Dx of liver metastases).
- N=4 had laparotomy and showed the presence of micronodular peritoneal disease in N=2.
- All pts had severe pain during TACE (probably due to arteritis caused by dacarbazine, requiring anaesthesiologic sedation).

AUTHORS’ CONCLUSIONS: Although limited to only nine cases, our experience suggests that TACE is effective in the temporary control of liver metastases, and it may increase the patients’ survival time; unfortunately, it cannot avoid the rapid development of extrahepatic disease.

**Additional comments on quality of study**

Applicable/direct population; small study size; shorter follow-up than some other studies.
N=20/23 untreated pts with metastatic UM (histologically verified) were evaluable

INTERVENTION: Chemotherapy with BOLD (bleomycin+vincristine+lomustine+dacarbazine) with intercycle alpha interferon-2b.

REGIMEN: dacarbazine (DTIC), 200 mg/m² IV on days 1-5; vincristine, 1 mg/m² (not to exceed 2 mg) IV on days 1 and 4; bleomycin, 15 mg IV days 2 and 5; lomustine (CCNU), 80 mg orally on day 1; and alpha interferon-2b, 3 x 10⁶ IU subcutaneously on days 8, 10, 12, 15, 17, 19.

FOLLOW-UP: A cycle was 28 days, and patients were reevaluated after every 2 cycles.

OUTCOMES: Objective tumor response and toxicity.

RESULTS:
- Objective responses: n=4 (RR = 20%).
- Hematologic toxicity: modest compared to some other combination chemotherapy regimens in common use.
- Neurotoxicity: frequently observed, but was seldom severe.
- Other: n=3 pts had unexpected and unpredictable severe pulmonary toxicity (unclear etiology).

AUTHORS’ CONCLUSION: The regimen of BOLD+interferon is active in the treatment of metastatic UM The precise role of the regimen has to be defined in light of its toxicity, particularly the unpredictable pulmonary toxicity. The pattern of occurrence of these pulmonary events is most consistent with either an acquired hypersensitivity reaction or a cumulative toxic effect of 2 or more of the agents. Patients considered for treatment with this regimen must be judiciously selected. Those with no clear contraindications may benefit from a trial of this regimen, but they must be monitored closely.

Additional comments on quality of study: reasonable sample size (as rare condition); applicable/direct population

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<th>Study Type</th>
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<td>Outcomes recorded</td>
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Matrix metalloproteinase-2 (MMP-2) immunoreactive protein--a new prognostic marker in uveal melanoma?


Study Type | Case Series |
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<td>Number of patients</td>
<td>Patient Characteristics</td>
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<td>Outcomes recorded</td>
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</table>
Results

Applicable? Conclusions

Prognostic study - presence and effect of MMP-2 (matrix metalloproteinase-2), gelatinases A and B, and the tissue inhibitor of metalloproteinases (TIMPs)

N=29 UM (52% men, mean age of all = 61 years, range 23-75 yrs).
Duration of follow-up = minimum 54 months
Primary Tx = enucleation of the affected eye.
N=15 died during follow-up, and N=1 excluded from study due to another type of cancer 55mths post-enucleation.

Tissue samples of tumours were analysed immunohistochemically, and vitreous samples were analysed by ELISA.

RESULTS:
- 49% of the UM were MMP-2 positive (immunoreaction) in melanoma cells, the epithelioid cells showing the most frequent staining.
- No correlation between positivity of MMP-2 staining and size of primary tumour, gender or age.
- Expression of MMP-2 was associated with poor prognosis: 5-year overall survival rate for MMP-2 positive was significantly worse vs. negative cases (49% vs. 86%; p=0.02).
- Positive immunostaining correlated significantly with the occurrence of visceral metastases (p<0.05).
- A patient group at high risk of metastatic disease was identified; only 38% of pts with a MMP-2-positive non-spindle cell uveal melanoma survived for 5 years.
- Analyses of MMPs or TIMPs in the vitreous body had no prognostic value.
- Positive immunostaining for MMP-2 was observed in the retinal pigment epithelium, corneal epithelium, and fibroblasts in the ciliary body and choroid.

AUTHORS' CONCLUSION: Immunohistochemical analysis of MMP-2 may help to predict a risk of metastasis in uveal melanoma

Applicable/direct population; long follow-up

Additional comments on quality of study
Q2. What is the most robust prognostication (known prognostic factors for survival)

Grading: 1+  
Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

9344  Phase II study of selumetinib versus temozolamide in advanced uveal melanoma.  2013
Carvajal R.  
Journal of Clinical Oncology Abstract #CRA9003

Study Type  
Randomised Controlled Trial

Number of patients  
N=80 (Sel = 39, TMZ = 41)

Patient Characteristics  
Inclusion/Exclusion

Study aim/Intervention  
Sel = selumetinib 75 mg BID, for 5 days in 28-day cycles

Comparators  
TMZ = temozolamide-hyd-sulfate 150 mg/m2 daily, for 5 days in 28-day cycles

Follow-up  
Tumor assessment occurred every 4 wks for 8 wks and then every 8 wks using RECIST 1.1. Results given for interim analysis.

Outcomes recorded  
Progression free survival (PFS); Overall survival (OS); Response rate (RR).

Results  
SEL: 11/39 (28%) experienced grade (gr) 3 toxicity (tox) manageable with dose modification (5 CPK elevation, 3 LFT elevation, 1 rash, 1 lymphopenia, 1 edema). TMZ: 1/41 (2%) experienced gr 3 tox (neutropenia). No gr 4/5 tox occurred. 28 pts on sel underwent paired tumor biopsies with inhibition of pERK and cyclinD1 observed by Western blot at day 14. At interim analysis (9/25/12), 55 pts were evaluable with 45 progression events and 16 deaths. Sel (n=27): median PFS 16 wks (95% CI 8-30.9), RR 11%, median OS 11.8 months (95% CI 4.8-not reached). TMZ (n=28): median PFS 4 wks (95% CI 3.7-15), RR 0%, median OS 4.7 months (95% CI 4.3-14.3). TMZ→sel (n=25): median PFS 8.1 wks (95% CI 7-15), RR 0%.

Applicable?  
Yes.

Conclusions  
CONFEERENCE ABSTRACT SO NOT ABLE TO ASSESS FULL METHODOLOGICAL DETAILS, SO HAVE ANSWERED SOME QUESTIONS AS 'NOT REPORTED' DUE TO THIS.

Additional comments on quality of study  
Conclusions: Sel is the first drug to ever show improved clinical activity in UM relative to TMZ. Sustained target inhibition is observed with sel.

9343  A phase III random assignment trial comparing percutaneous hepatic perfusion with melphalan (PHP-mel) to standard of care for patients with hepatic metastases from metastatic ocular or cutaneous melanoma  2010
### Percutaneous hepatic perfusion

**Study Type**
Randomised Controlled Trial

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Inclusion/Exclusion</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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</thead>
<tbody>
<tr>
<td>Percutaneous hepatic perfusion with metaphalan (PHP-mel): N=44; Standard care/best available care (BAC): N=49</td>
<td>Percutaneous hepatic perfusion (metaphalan)</td>
<td>Standard care (BAC)</td>
<td>Yes. Follow-up staging evaluated at 6-8 week post-baseline.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Results**

ITT based survival analysis (Kaplan-Meier method). H-PFS = hepatic preogresion free survival. Response rate = using RECIST criteria.

- **Median H-PFS:**
  - PHP-mel = 245 days (CI:136, 267) vs. BAC = 49 days (CI:43, 68); p<0.001.
  - Overall response rate:
    - PHP= 34.1 % (15/44) (CI: 20.5, 49.9) vs. BAC = 2.0 % (1/49) (CI: 0.1, 10.9); p<0.001.

Upon hepatic progression, crossover to PHP occurred in 27 patients (55%) randomized to BAC.

**Conclusions**

For patients with metastatic melanoma to the liver, H-PFS is significantly improved with PHP-mel versus best available care.

**Grading:** 3  
*Non-analytic studies (for example, case reports, case series)*

1858  Protracted survival after resection of metastatic uveal melanoma

Aoyama T, Mastrangelo MJ, Berd D, Nathan FE, Shields CL, Shields JA, Rosato EL, Rosato FE, Sato T,

**Cancer**

89 1561 1568
Results

Applicable? no.

Conclusions

Additional comments on quality of study

Small single centre retrospective series.

131 Outcome of patients following hepatic resection for metastatic cutaneous and ocular melanoma 2011 Mar

Study Type Case Series
Number of patients 6 OM patients
Patient Characteristics Inclusion/Exclusion
Study aim/Intervention
Comparators No comparative data to systemic therapy
Follow-up Median survival similar to other published series (24.6 mths) suggesting some consistency in outcomes across surgical series.
Outcomes recorded

Results

550 Hepatic metastasis from uveal melanoma: angiographic pattern predictive of survival after hepatic arterial chemoembolization 2009 May
### Study Type
- **Study aim/Intervention**
  - HACE - cisplatin, doxorubicin + mitomycin C
  - Further treatment if residual disease or disease progression

### Comparators
- Mean no. Of treatment - 1.9 for infiltrative, 2.9 for nodular
- Median survival (months) - 3.7 for infiltrative, 12.7 for nodular
- A few had subsequent systemic chemo/resction/radiofreq ablation
- Improved survival linked to angiographic pattern or dose response to HACE?

### Additional comments on quality of study

#### Results

**Applicable?** Helpful

**Conclusions**

**Prognostic factors in MUM.**

**Study Type**
- **Case Series**
  - **Patient Characteristics**
    - **Inclusion/Exclusion**
    - **Study aim/Intervention**
    - **Comparators**
    - **Follow-up**
    - **Outcomes recorded**

**Number of patients**
- **1470**

**Eskelin S, Pyrhonen S, Hahka KM, Tuomaala S, Kivela T,**

**Cancer**

**97**

**465**

**475**

**2003 Jan 15**

**Modelling in 91pts from 1985-2000. KP, largest diameter, serum ALP independent prognostic factors. 3 cohorts stage 4a/b/c with OS 14.9, 8.9, 2mths**

**Working formulation defined**
### Results

**Applicable?** Retrospective review

**Conclusions**

**Additional comments on quality of study**

<table>
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<th>Number of patients</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>112</td>
<td></td>
<td>prognostic factors - Retrospective R0 resection</td>
<td>site of mets, number of mets and DFI were independent Prog factors for OS. Prolonged survival after complete resection of metastases from intraocular melanoma.</td>
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#### Patient Characteristics

- **Inclusion/Exclusion**
- **Study aim/Intervention**
- **Comparators**
- **Follow-up**
- **Outcomes recorded**

#### Study Type

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#### Results

**Applicable?** Yes

**Conclusions**

**Additional comments on quality of study**

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<th>Number of patients</th>
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<tr>
<td>1177</td>
<td>Prognostic factors of liver metastases from uveal melanoma</td>
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<td>243 985 993</td>
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<tr>
<td>Number of patients</td>
<td>63</td>
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<td>Patient Characteristics</td>
<td>Inclusion/Exclusion</td>
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<tr>
<td>Study aim/Intervention</td>
<td>systemic chemo (dacarbazine/fotemustine/phase 1/2 trials/supportive care)</td>
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<tr>
<td>Comparators</td>
<td>resection (microscopically complete/incomplete/macroscopically incomplete)</td>
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<td>Follow-up</td>
<td>Two independent factors of OS ≤10 mets &amp; no ciliary body involvement of primary</td>
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<td>Outcomes recorded</td>
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</table>

**Results**

**Applicable?** Retrospective.

**Conclusions**

Additional comments on quality of study

Mariani P, Piperno NS, Servois V, Berry MG, Dorval T, Plancher C, Couturier J, Levy GC, Lumbroso LR, Desjardins L, Salmon RJ,

European Journal of Surgical Oncology

35 1192 1197

Surgical management of liver metastases from uveal melanoma: 16 years’ experience at the Institut Curie

2009 Nov

Compares 543 pts with liver mets treated with systemic chemo (dacarbazine/fotemustine/phase 1/2 trials/supportive care) with 255 who underwent resection (microscopically complete/incomplete/macroscopically incomplete).

Macro incompletes had intra hepatic artery dacarbazine/fotem
### 7447: Characterization of computed tomography scan abnormalities in patients with biopsy-proven hepatic metastases from uveal melanoma


**Study Type:** Diagnostic  
**Number of patients:** 76 biopsy proven metastatic patients referred to a single centre. 505 patients referred  
**Patient Characteristics**  
Inclusion/Exclusion  
CT liver but with mix of contrast and chest slices  
**Study aim/Intervention**  
no reference but CT contrast/MRI contrast standard  
**Comparators**  
**Follow-up**  
**Outcomes recorded**  
The study potentially identifies clinical/imaging prognostication where relates tumour volume to prognosis based upon max tumour diameter (100cm²), ascites and hepatomegaly.

### Results

Median survival 14 months (resection) vs 8 months (no resection)

### Applicable?

Partly

**Conclusions**

However likely selection bias  
No details on chemo cycles, which 8 had RFA etc

### Additional comments on quality of study

Retrospective, single centre, large numbers

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### 336: Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease


**Study Type:** Diagnostic  
**Number of patients:** 76 biopsy proven metastatic patients referred to a single centre. 505 patients referred  
**Patient Characteristics**  
Inclusion/Exclusion  
CT liver but with mix of contrast and chest slices  
**Study aim/Intervention**  
no reference but CT contrast/MRI contrast standard  
**Comparators**  
**Follow-up**  
**Outcomes recorded**  
The study potentially identifies clinical/imaging prognostication where relates tumour volume to prognosis based upon max tumour diameter (100cm²), ascites and hepatomegaly.

### Results

not specified

### Applicable?

No, the study describes CT characteristics in metastatic disease

**Conclusions**

Yes, but the study incorporates late stage disease with high tumour burden

---
Retrospective case series of liver resection with median OS 29.4mths and PFS 8.8mths. 2 and 5 year OS 61.5 and 20%, respectively. Apparent consistency across surgical trials. This study provides preliminary support for the concept that surgery associated with improved PFS and OS than reported systemic trials (not comparable) This requires a controlled trial.

### Results

**Additional comments on quality of study**

uncontrolled, single centre and retrospective

217 Metastatic uveal melanoma: is there a role for conventional chemotherapy? - A single center study based on 58 patients. [Review]


### Study Type

Case Series

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td></td>
<td>evaluating chemotherapy and supportive care.</td>
<td>Non randomised.</td>
<td></td>
<td>Prognostic factors including liver metastases number &gt; 5 and ECOG 1-2 vs 0 on multivariate analysis.</td>
</tr>
</tbody>
</table>

No.

Conclusions

Applicable? No.

Additional comments on quality of study

uncontrolled, single centre and retrospective
Results

Applicable? No
Conclusions Provides data on possible prognostic factors but no comparison of treatment effect

Additional comments on quality of study single centre retrospective case
series only

1218 'Melanoma inhibitory activity' (MIA): a promising serological tumour marker in metastatic uveal melanoma

Study Type Case Series
Number of patients 305 patients undergoing screening
LFTs/USS. Included 20 patients with mets.

Comparators Tumour marker for met disease:

Outcomes recorded

Results MIA significantly increased in met disease (p<0.001)

Applicable? unhelpful, small series
Conclusions

Additional comments on quality of study Single prospective study

1219 Variates of survival in metastatic uveal melanoma

Study Type Case Series
Number of patients 1218

Comparators

Outcomes recorded

Results

Applicable? Variates of survival in metastatic uveal melanoma
Conclusions

Additional comments on quality of study Single prospective study

1219 Variates of survival in metastatic uveal melanoma

Study Type Case Series
Number of patients 1218

Comparators

Outcomes recorded

Results

Applicable? Variates of survival in metastatic uveal melanoma
Conclusions

Additional comments on quality of study Single prospective study
Prognostic factors in MUM:

**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

**Applicable?**

**Conclusions**

**Additional comments on quality of study**

- retrospective series, single centre.

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**Study Type**

Case Series

**Number of patients**

119pts

**Results**

5 factors independent for OS (lung soft tissue disease as first organ, surgery/intrahepatic therapy, female, <60yrs and DFI).

---

**Study Type**

Case Series

**Number of patients**

63/602 USS screened pts with liver mets.

**Results**

22% R0 resection rate with median OS 25mths vs 11mths (BSC/chemo)

Univariate analysis: >70yrs, number of mets <10, R0 resection

---

**Study Type**

Case Series

**Number of patients**

1220

**Results**

20% R0 resection rate with median OS 25mths vs 11mths (BSC/chemo)

1983-1996, single series
### Treatment of liver metastases from uveal melanoma by combined surgery-chemotherapy

**Study Type**: Case Series  
**Number of patients**: 75  
**Study aim/Intervention**: Intra-arterial chemotherapy post surgical resection of liver mets in OCM.  
**Comparators**: surgery-chemotherapy  
**Results**: Marked improvement in survival following complete liver met resection and chemotherapy (fotemustine and/or DTIC/platinum (p<0.001) from 9-10 months to 22 months. No benefit of incomplete resection and/or chemo compared to historical controls (~9 months)  
**Conclusions**: Interesting study indicating that aggressive surgical approach is better. Role of chemotherapy uncertain but needs a randomised study.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Cohort</th>
</tr>
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<tbody>
<tr>
<td>Number of patients</td>
<td>48 mets*</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Microcirculation and tumor-infiltrating macrophages in choroidal and ciliary body melanoma and corresponding metastases</td>
</tr>
<tr>
<td>Study aim/Intervention</td>
<td>Micro vessel density in liver mets prognostic for OS</td>
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<tr>
<td>Comparators</td>
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<td>Follow-up</td>
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<td>Outcomes recorded</td>
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</tbody>
</table>

Applicable? Retrospective histology review.

Conclusions

Additional comments on quality of study
**Q1. What is optimal staging/imaging**

<table>
<thead>
<tr>
<th>Grading:</th>
<th>1++</th>
<th>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1723</td>
<td>Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15</td>
<td>2001</td>
</tr>
<tr>
<td>Wilson et al</td>
<td>Archives of Ophthalmology</td>
<td>119 670 676</td>
</tr>
</tbody>
</table>

**Results**

Of 1003 patients enrolled, 457 died during the study period. Of these disease status was reviewed for 435. 62% had confirmed metastases, and a further 29% were suspected of having metastases. Sites: liver 93%, lung 24%, bone 16%, with multi-site in 87%.

**Conclusions**

This is a retrospective analysis of prevalence of metastatic disease at death of patients enrolled in the COMS study. This study does not directly answer one of the questions, but does demonstrate the high rate of multi-site disease in these patients, which is important when making decisions regarding local treatment.

**Additional comments on quality of study**

Rachel comment: data from the COMS RCT - probably combined arms, but still from RCT.

| 2+ | Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal |
| --- | --- | --- | --- | --- |
| 640 | Limited value of 18F-FDG PET/CT and S-100B tumour marker in the detection of liver metastases from uveal melanoma compared to liver metastases from cutaneous melanoma Predictive power of screening tests for metastasis in uveal melanoma. | 2009 |

**Study Type**

- Randomised Controlled Trial
- Cohort
**Results**

Total 27 mets, 50% FDG negative
4 pts had extrahepatic mets (lung, bone, LN, peritoneal) - all FDG +ve

Serum S-100B taken in 6 pts, 4 were normal, 2 were raised

**Applicable?** Partly

**Conclusions** Retrospective, single centre

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**Grading:** 3  
**Non-analytic studies (for example, case reports, case series)**

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<tr>
<th>Study Type</th>
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<td>Number of patients</td>
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<td>Study aim/Intervention</td>
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<td>Outcomes recorded</td>
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<th>Case Series</th>
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<tr>
<td>Number of patients</td>
<td>Patient Characteristics</td>
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<td></td>
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<td>Outcomes recorded</td>
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</tbody>
</table>

**Results**

n = 40 pts with liver metastases from UM
Undergoing Selective internal radiation therapy (SIRT) with 90yttrium (Y)-resin microspheres.

- FDG PET performed
- Best radiographic response of hepatic metastasis was determined on MRI studies obtained every 3 mos. after Tx.
FTV = functional tumour volume; TLG = total lesion glycolysis.

**RESULTS:**

- Liver only metastases (n = 13).
- Median follow-up= 8.0 mos. (range, 1.0-48.5).
- Best radiographic response was: complete response in 2% (n = 1), partial response in 13% (n = 5), stable disease in 35% (n = 14), progressive disease in 33% (n = 13) and indeterminate in 17% (n = 7).
- N = 33 pts had progression of hepatic metastases (median PFS 5.6 mos; range, 1.1-40.7)
- N = 30 pts died with a median OS of 9.9 mos. (range, 2.4-51.7).
- Pts who had pretreatment FTV<100 cc (n = 25) vs. those with pretreatment FTV<=100 cc (n = 15) had longer median survival time (MST) (17.5 vs. 7.6 mos., p < 0.0001, hazard ratio [HR] = 0.13, 95% CI 0.05 to 0.33) and PFS (8.0 vs. 4.7 mos., p = 0.002, HR = 0.20, 95% CI 0.07 to 0.55).
- Pts who had pretreatment TLG<500 cc (n = 27) had longer MST (17.0 vs. 7.4 mos.; p < 0.0001, HR = 0.06, 95% CI 0.02 to 0.18) and PFS (8.1 vs. 3.8 mos.; p = 0.0006, HR = 0.12, 95% CI 0.04 to 0.41) than those with pretreatment TLG<=500 cc (n = 13).

CONCLUSIONS: Pretreatment FTV and TLG were predictive of OS and PFS. These values may be useful as criteria for patient selection for treatment with 90Y SIRT in patients with liver metastases from uveal melanoma.
Yes

N=19 pts with UM (N=10 had prev had melanoma Tx: enucleation or tumour surgery)
F-FGD PET/CT conducted
AIM: To assess the correlation between Standardized Uptake Value (SUV) of primary tumor against the presence of metastatic spread at the time of the study.

RESULTS:
- 10 patients had metastatic lesions (52.6% of total); N=7 WERE LIVER

CONCLUSION:
- PET/CT using F-FDG is shown as an effective exploration in detecting distant metastases in patients with UM
- The most common location was the liver
- The relationship between the value of SUV in the primary tumor and metastatic spread were not statistically significant, although the scarcity of the sample cannot allow us to state this with certainty

UNABLE TO GET FULL PAPER SO INFO IS FROM ABSTRACT

Additional comments on quality of study
Small study, direct population (UM), retrospective analysis

9231 Characteristics and survival in patients with metastatic uveal melanoma: Analysis of a referral center cohort

Data from abstract only as full paper not published (this is a conference abstract)
- Estimated median survival analyzed = 8.4 months (range 0 to 76).
- Survival > 2yrs = 10% of pts
- Diffuse organ metastases = 89% of pts, liver involved in 96%
- Surgical resection of single metastases performed = N=5 pts
- Received at least two different systemic therapies = 54% of pts.

PROGNOSTIC FACTORS FOR SURVIVAL - MULTIVARIATE ANALYSIS:
- AP (HR: 3.5)
- Bilirubin (HR: 2.7)
- LDH (HR: 2.0)
- 22% of pts had elevated bilirubin at initial presentation and median survival = 3.1 mths as compared to 9.2 mths in patients with normal bilirubin.

Conclusions: The overall patient cohort still had poor outcome, but a proportion of patients was included in one or several subsequent experimental treatment protocols. Only very few patients were candidates for surgery. Despite of ultrasonography screening, more than 20% of patients still presented with evidence for liver failure, which rendered them unsuitable for testing of novel therapies.

CONFERENCE ABSTRACT - not fully published paper

Additional comments on quality of study
Direct/applicable population; good sample size, a lot of details given even in abstract.

Study Type
Diagnostic

Number of patients
15

Patient Characteristics
Pts with suspected liver mets on USS/CT underwent MRI and FDG-PET preop (1-31d prior). Intraop findings + intraop USS compared to PET + MR.

Study aim/Intervention
Reported (MRI by 2 clinicans, PET not stated) without knowledge of the other mode’s result but knowing liver mets suspected on USS/CT.

Results
12 of 15 pts underwent resection, 28 lesions resected, 9 were <5mm

in 1 pt, 4 lesions showed up on MR not on PET, 3 other lesions in 3 pts similarly on MR not on PET

1 FP for MR, 0 for PET
PPV: MR 98%, PET 100%
Sensitivity for lesions >5mm: 100% for MR, 61% for PET

All lesions not detected by MR were capsular 1-2mm lesions
PET did not identify 2 >10mm lesions, and 5 intraparenchymal nodules 5-10mm

483 Preoperative staging of liver metastases from uveal melanoma by magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET) 
Servois V, Mariani P, Malhaire C, Petras S, Piperno NS, Plancher C, Levy GC, Lumbroso LR, Desjardins L, Salmon RJ, European Journal of Surgical Oncology 36 189 194
Helpful for staging

Suggest MRI is better, and appears to sometimes suggest miliary (inoperable) disease (though no data for this)

Additional comments on quality of study
**Q3. What is the optimal management of with systemic metastases?**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
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</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td></td>
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<tr>
<td><strong>Patient Characteristics</strong></td>
<td>Study aim/Intervention</td>
</tr>
<tr>
<td><strong>Inclusion/Exclusion</strong></td>
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<tr>
<td>171</td>
<td>First line UM</td>
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<tr>
<td><strong>Comparators</strong></td>
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<tr>
<td>Ia vs iv chemo</td>
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<td><strong>Follow-up</strong></td>
<td></td>
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<tr>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes recorded</strong></td>
<td></td>
</tr>
<tr>
<td>RR, PFS, OS</td>
<td></td>
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</tbody>
</table>

**Results**

RCT with no OS. NO OS gain. Improved RR, PFS

**Applicable?** Yes

**Conclusions**

Additional comments on quality of study: Good

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**Randomized phase III trial of intravenous (IV) versus hepatic intra-arterial (HIA) fotemustine in patients with liver metastases from uveal melanoma: Final results of the EORTC 18021 study**


Journal of Clinical Oncology

30

Study Type

Randomised Controlled Trial

Results

No OS gain. Improved RR, PFS

---

**Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial.**


Annals of Oncology

25 272 276

Study Type

Randomised Controlled Trial

Results

No OS gain. Improved RR, PFS
### Grading: 1+  
**Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**

<table>
<thead>
<tr>
<th>1068</th>
<th>A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006 Dec</td>
<td>17 1826 1829</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
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<table>
<thead>
<tr>
<th>Number of patients</th>
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</table>

<table>
<thead>
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<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion</td>
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</tbody>
</table>

**Results**

**Additional comments on quality of study**

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<table>
<thead>
<tr>
<th>9334</th>
<th>Chemosaturation therapy with percutaneous hepatic perfusions of melphalan versus standard of care in patients with hepatic metastases from melanoma: A randomized multicenter phase 3 study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zager J, Nutting C,</td>
<td>Journal of Vascular and Interventional Radiology</td>
</tr>
<tr>
<td>2012</td>
<td>23</td>
</tr>
</tbody>
</table>
### Results

**Study Type**
Randomised Controlled Trial

**Number of patients**
93

**Patient Characteristics**
Liver UM

**Study aim/Intervention**
Regional vs BAC

**Comparators**
PHP v BAC

**Follow-up**
RR, H.PFS, OS

**Outcomes recorded**
RCT phase III trial with no OS gain. 6.7mth HPFS vs 1.6mth

---

**Study Type**
Randomised Controlled Trial

**Number of patients**
28 cross over pts

**Patient Characteristics**
UM

**Study aim/Intervention**
PHP post BAC

**Comparators**

**Follow-up**
RR, OS

**Outcomes recorded**
RR/PFS gain but not OS. RR, OS in cross over

---

**Applicable?**
Yes

**Conclusions**

**Additional comments on quality of study**
Good

---

**Grading:**
2+  
*Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal*
Non-randomised data but suggestive of liver-directed therapies being important in disease management.

Need for OCM-specific trials of chemotherapy approaches.

Patient Characteristics

Inclusion/Exclusion

Study aim/Intervention

Comparators

Follow-up

Outcomes recorded

Applicable?

Conclusions

Additional comments on quality of study

Study Type

Cohort

Study of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors

Bedikian AY, Legha SS, Mavligit G, Carrasco CH, Khorana S, Plager C, Papadopoulos N, Benjamin RS,

Cancer

1995 Nov 1

76 1665 1670

Number of patients

201 patients with OCM treated between 1968-1991

Results

<1% response rate in OCM with systemic chemotherapy contrasting with 36% RR with platinum-based liver chemoembolisation. Chemoembolization responders survived significantly longer than the chemoembolization nonresponders (median, 14.5 vs. 5 months; P = 0.003) or the patients who received systemic chemotherapy (median, 14.5 vs. 5 months; P = 0.003).

Non-randomised data but suggestive of liver-directed therapies being important in disease management.

Need for OCM-specific trials of chemotherapy approaches

Additional comments on quality of study

Study of uveal melanoma metastatic to the liver: a review of the M. D. Anderson Cancer Center experience and prognostic factors

Bedikian AY, Legha SS, Mavligit G, Carrasco CH, Khorana S, Plager C, Papadopoulos N, Benjamin RS,
Phase II Trial of Sorafenib in Combination with Carboplatin and Paclitaxel in Patients with Metastatic Uveal Melanoma: SWOG S0512


Study Type: Cohort
Number of patients: 25
Stage IV UM

Study aim/Intervention: Chemo/sorafenib

Comparators: Chemo/sorafenib

Follow-up: Until death
Outcomes recorded: RR, PFS/OS

Results: No benefit

Applicable? Phase II trial

Conclusions

Additional comments on quality of study: Good

Metastatic melanoma from intraocular primary tumors: the Southwest Oncology Group experience in phase II advanced melanoma clinical trials

Flaherty LE, Unger JM, Liu PY, Mertens WC, Sondak VK, American Journal of Clinical Oncology 21 568 572

Study Type: Case-Control
Number of patients: 64 patients with OCM

Study aim/Intervention: OCM compared to cutaneous melanoma outcomes for chemotherapy

Comparators: OCM compared to cutaneous melanoma outcomes for chemotherapy

Follow-up: Until death
Outcomes recorded: Survival and response rates to chemo (DTIC, Cis and IL-2)

Results: 5% RR in OCM with liver mets (7% for cutaneous melanoma group). No difference in survival between OCM and cutaneous melanoma (5.2 vs 4.8 months). Higher response rate noted in OCM with extrahepatic disease only (43% RR)
OCM patients should be included in trials of chemo for other melanoma patients, since frequency of response is similar. New approaches are required.

Additional comments on quality of study
7 phase II SWOG trials in the 1980s

Activity of cabozantinib (XL184) in metastatic melanoma: Results from a phase II randomized discontinuation trial (RDT)

Journal of Clinical Oncology

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of patients</th>
<th>Patient Characteristics</th>
<th>Study aim/Intervention</th>
<th>Comparators</th>
<th>Follow-up</th>
<th>Outcomes recorded</th>
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<tbody>
<tr>
<td>Cohort</td>
<td>77 (30% ocular)</td>
<td>Mixed melanoma</td>
<td>cabozantinib</td>
<td>n/a</td>
<td>RR/PFS</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>placebo</td>
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</tbody>
</table>

Results Possible activity, 48% ‘response’

Additional comments on quality of study
Good

Ipilimumab in the treatment of uveal melanoma: The Memorial Sloan-Kettering Cancer Center experience

Journal of Clinical Oncology

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<td>UM</td>
<td>ipi</td>
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<td>RR/OS</td>
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</table>

Applicable? Phase II randomised discontinuation

Conclusions

Additional comments on quality of study

Good
### BEVATEM: Phase II single-center study of bevacizumab in combination with temozolomide in patients (pts) with first-line metastatic uveal melanoma (MUM): First-step results

**Piperno NS, Servois V, Bidard F, Mariani P, Plancher C, Asselain B, Vago AN, Desjardins L,**

*Journal of Clinical Oncology* 2012

<table>
<thead>
<tr>
<th>Study Type</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>Patient Characteristics</td>
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<tr>
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<td>Inclusion/Exclusion</td>
</tr>
<tr>
<td>17</td>
<td>UM Biological and chemo</td>
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</table>

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<tr>
<td>3/17 6mths PFS</td>
<td></td>
<td>PFS at 6mths</td>
<td></td>
</tr>
</tbody>
</table>

### A two-cohort phase II clinical trial of gemcitabine plus treosulfan in patients with metastatic uveal melanoma

**Schmittel A, Schuster R, Bechrakis NE, Siehl JM, Foerster MH, Thiel E, Keilholz U,**

*Melanoma Research* 2005 Oct

<table>
<thead>
<tr>
<th>Results</th>
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<td>1226</td>
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</table>

| Number of patients | Patient Characteristics |
|                   | Inclusion/Exclusion |
|                   | UM                  |

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</table>

**Applicable?** Single centre retrospective cohort

**Conclusions**

**Additional comments on quality of study** Good
### Study Type
Cohort

### Number of patients
33pts.

### Patient Characteristics

### Study aim/Intervention
Systemic therapy for MUM:

### Comparators

### Follow-up

### Outcomes recorded

#### Results
1 PR, prolonged stabilisation with higher dose treo. 47.1% 1 yr OS vs 7.1%.

#### Applicable?
Hypothesis generating only

#### Conclusions

Additional comments on quality of study
non randomised, 2 cohort study

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### Additional study

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<thead>
<tr>
<th>Study Type</th>
<th>Cohort</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<tr>
<td>Patient Characteristics</td>
<td>Melanoma mixed</td>
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<td>Study aim/Intervention</td>
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<td>Comparators</td>
<td>OS</td>
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<td>Follow-up</td>
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<tr>
<td>Outcomes recorded</td>
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</tbody>
</table>

#### Additional comments on quality of study
Good

Aflibercept (VEGF Trap) in inoperable stage III or stage IV melanoma of cutaneous or uveal origin 2011

Tarhini AA, Frankel P, Margolin KA, Christensen S, Ruel C, Shipe SJ, Gandara DR, Chen A, Kirkwood JM, Clinical Cancer Research

OS 16.3mths
<table>
<thead>
<tr>
<th>Grading: 2-</th>
<th>Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*</th>
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<tr>
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<td>Inclusion/Exclusion</td>
<td>UM pre-treated</td>
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<td>Study aim/Intervention</td>
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**Results**

3/7 protected SD up to 20mths. MIA, S100 correlation

**Applicable?** No

**Conclusions**

Additional comments on quality of study

Poor

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<tr>
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<td>'benefit'</td>
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<td>Outcomes recorded</td>
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**Results**

2 clinical benefit

**Applicable?** No

**Conclusions**

Additional comments on quality of study

Poor
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<tr>
<td>Register trial of sorafenib (S) for patients (pts) with metastatic uveal melanoma (metUvMel)</td>
<td>2011</td>
<td>62</td>
<td>UM</td>
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<td>2 dose groups</td>
<td>OS, TTP</td>
<td>10.8mths vs 14 mths OS</td>
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<td>Additional comments on quality of study</td>
<td>Poor</td>
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<tr>
<td>1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) chemoembolization (TACE) for treatment of bulky uveal melanoma (UM) hepatic metastases</td>
<td>2013</td>
<td>50</td>
<td>Bulky liver mets UM</td>
<td>Regional chemo</td>
<td>No</td>
<td>RR, PFS, OS</td>
<td>3 PR</td>
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</table>

Scheulen ME, Nokay B, Richly H, Hoffmann AC, Kalkmann J, Stattaus J, Bornfeld N, Molecular Cancer Therapeutics Conference 10
Cisplatin, gemcitabine and treosulfan is effective in chemotherapy-pretreated relapsed stage IV uveal melanoma patients


Results
6 + 12 months disease progression free survival was both 8% variable extrahepatic mets

Applicable? no

Treatment of disseminated ocular melanoma with sequential fotemustine, interferon alpha, and interleukin 2

### Phase II trial of tirapazamine combined with cisplatin in chemotherapy of advanced malignant melanoma


#### Study Type
Case Series

#### Number of patients
6 patients with OCM

#### Study aim/Intervention
Tirapazamine-cisplatin combination

#### Results
No responses in OCM seen (compared to 33% RR in cutaneous melanoma); small number of OCM patients. Non-randomised study.
### Phase II Evaluation of Temozolomide in Metastatic Choroidal Melanoma

**Study Type:** Case Series

**Number of patients:** 14 pts.

**Study aim/Intervention:** Systemic therapy in MUM.

**Results:** No response, PFS 1.8 mths, OS 6.7 mths

<table>
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<tr>
<th>Applicable?</th>
<th>Conclusions</th>
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Additional comments on quality of study: Single centre series

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### A Pilot Study with Vincristine Sulfate Liposome Infusion in Patients with Metastatic Melanoma

**Study Type:** Case Series

**Number of patients:** 27 mixed melanoma, 4 were UM.

**Results:**

<table>
<thead>
<tr>
<th>Applicable?</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>No</td>
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</tbody>
</table>

Additional comments on quality of study: Single centre, non-randomised, pilot study
A phase II evaluation of bexarotene (Targretin) capsules in patients with metastatic melanoma 2000 Jul

Bedikian AY, Plager C, Papadopoulos N, Ellerhorst J, Smith T, Benjamin RS, Oncology Reports 7 883 886

Study Type Case Series
Number of patients 4
Results no response

Applicable? Phase 2
Conclusions

Additional comments on quality of study

Ipilimumab in pretreated patients with metastatic uveal melanoma: Safety and clinical efficacy 2012


Study Type Case Series
Number of patients 2 stable disease patients and a further with delayed response after progression.

Results

Very preliminary data providing toxicity and feasibility information only
### Applicable
No expanded access programme in small series of patients managed across multiple sites.

### Additional comments on quality of study

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<thead>
<tr>
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<tr>
<td>1605</td>
<td>Phase II trial of 9-nitrocamptothecin (RFS 2000) for patients with metastatic cutaneous or uveal melanoma</td>
<td>Patient Characteristics</td>
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<td></td>
<td>Ellerhorst JA, Bedikian AY, Smith TM, Papadopoulos NE, Plager C, Eton O,</td>
<td>Anti-Cancer Drugs</td>
<td>2002 Feb</td>
<td>13</td>
<td>169</td>
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### Results

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### Additional comments on quality of study

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</table>
### Applicable?
No,

### Conclusions

**Additional comments on quality of study**

**single arm phase II trial**

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<th>Study Type</th>
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<tr>
<td>Number of patients</td>
<td>22 patients</td>
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**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

1 PR and 32% SD. Safety and toxicity. Provides preliminary data on PFS in metastatic setting.

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### Results

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### Applicable?
No,

### Conclusions

**Additional comments on quality of study**

**single arm phase II trial**

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<td>22 patients</td>
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**Patient Characteristics**

**Inclusion/Exclusion**

**Study aim/Intervention**

**Comparators**

**Follow-up**

**Outcomes recorded**

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Applicable? Conclusions
Tx: ipilimumab 3 mg/kg in week 1, 4, 7 and 10;
Population: N=22 unresectable metastatic UM pts. Pretreated (received at least one prior Tx regimen for metastatic disease). WHO performance status of 0, 1, or 2. 28-day interval since the last Tx.
Methods: retrospective data from pts in the named patient program (NPP) by the Dutch immunotherapy working group (WIN-O) in The Netherlands.
Follow-up: Median 177 days (6.3 months)

RESULTS:
Clinical benefit was defined as the response proportion of patients plus SD lasting longer than 24 wks.
Drop-outs:
- only n=12 (55%) completed all 4 infusions of Tx.
- of the remaining 10 pts, n=9 had to discontinue Tx due to clinical deterioration due to disease progression (two of them died) and one because of SAEs.

Of the 22 patients who received at least one ipilimumab infusion:
- n=13 showed progressive disease (PD)
- n=1 pt had a partial remission (PR).
- n=0 pts had complete remission (CR) or SD (stable disease), according to RECIST 1.1.
- n=8 pts were not evaluable (NE).
Following irRC (to capture delayed anti-tumor responses often observed with immunotherapy):
- n=12 pts with PD, n=1 with SD, n=1 with PR, and n=0 CRs.
At the time of manuscript preparation n=1 patient (4.5%) was still alive with ongoing SD (+16 mths).
The patient observing a PR was eligible for ipilimumab re-induction due to disease progression 7 mths after ipilimumab initiation. Unfortunately, the re-induction did not result in a renewed response.
Kaplan-Meier analyses show:
- median PFS of 2.9 months.
- median OS was 5.2 months
- 1-year survival of 27%.
Most adverse events were immune-related. All pts received corticosteroid Tx (1 mg/kg predisolone) after which immune-related AEs quickly resolved.

Additional comments on quality of study
Retrospective, directly applicable population, small sample size, short to reasonable follow-up (12 weeks and >24 wks for outcome of 'clinical benefit')
VERY HIGH MISING DATA / DROP OUTS
Results
Phase II no response. First and subsequent

Applicable? Yes
Conclusions

Additional comments on quality of study

1501 Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma

Study Type Case Series
Number of patients 24pts.
Patient Characteristics Systemic therapy in MUM
Inclusion/Exclusion
Study aim/Intervention No response. PFS 1.9mths, OS 10.6mths
Comparators OS correlated with HUCH prognostic model
Follow-up Outcomes recorded

Additional comments on quality of study EORTC multicentre phase II

10102 Clinical activity of ipilimumab for metastatic uveal melanoma: a retrospective review of the Dana-Farber Cancer Institute, Massachusetts General Hospital, Memorial Sloan-Kettering Cancer Center, and University Hospital of Lausanne experience.
Results

Applicable? Conclusions
Tx: Ipilimumab (n=34 had received 3 mg/kg ipilimumab; N=5 had received 10 mg/kg)
Population: N=39 pts with metastatic UM
Follow-up: median 50.4 weeks (12.6 mths)

RESULTS:
- WHO criteria Response rate (RR): 2.6% (12 wks), 2.6% (23 wks)
- WHO criteria combined response plus stable disease (SD) rate: 46% (12 wks), 28.2% (23 wks).
- There was 1 complete response and 1 late partial response (at 100 weeks after initial SD) for an immune-related RR of 5.1%.
- Immune-related AEs:
  - N=28 pts (71.8%). Included n=7 (17.9%) grade 3 and 4 events.
  - Immune-related AEs = more frequent in pts on 10 mg/kg ipilimumab vs. 3 mg/kg ipilimumab.
- Median overall survival (from 1st dose of ipilimumab): 9.6 mths (95% CI 6.3-13.4 mths; range 1.6-41.6 mths).
- Performance status, lactate dehydrogenase level, and an absolute lymphocyte count ≥ 1000 cells/μL at week 7 were associated significantly with survival.

AUTHORS' CONCLUSIONS: In this multicenter, retrospective analysis of 4 hospitals in the United States and Europe of patients with uveal melanoma, durable responses to ipilimumab and manageable toxicity were observed.

Additional comments on quality of study
Retrospective, directly applicable population, fairly small sample size, reasonable follow-up

10101 Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma.
Annals of Oncology 24 2911 2915

Results

Applicable? Conclusions
Tx: ipilimumab 3 mg/kg through an expanded access programme, every 3 weeks for four doses
Population: N=82 assessable pts with advanced UM
Follow-up: median 5.6 months

RESULTS:
- N=4 pts (5%) had an immune-related objective response
- n=24 pts (29%) had immune-related stable disease lasting ≥3 months for an immune-related disease control rate of 34%.
- Overall survival (OS): 6.0 mths
- Median progression-free survival (PFS): 3.6 mths.
- 1-year rates of OS and PFS: 31% and 11%.
- Safety profile of ipilimumab was similar to that in patients with cutaneous melanoma.

AUTHORS’ CONCLUSIONS: These data suggest ipilimumab 3 mg/kg is a feasible option in pre-treated patients with metastatic uveal melanoma. Evidence of disease control and a 1-year survival rate of 31% indicate the need for further investigation in randomised, controlled trials to determine the optimal timing and use of ipilimumab in this patient population.

Additional comments on quality of study
Prospective, directly applicable population, reasonable sample size, short to reasonable follow-up

1061 A prospective single arm phase II study of dacarbazine and treosulfan as first-line therapy in metastatic uveal melanoma

Study Type      Case Series
Number of patients 15pts.
Patient Characteristics Inclusion/Exclusion
Study aim/Intervention Systemic therapy in MUM:
Comparators
Follow-up
Outcomes recorded
Results No responses, PFS 12weeks, OS 30weeks

Applicable?
Conclusions

Additional comments on quality of study single centre series

763 O-Mel-Inib: a Cancero-pole Nord-Ouest multicenter phase II trial of high-dose imatinib mesylate in metastatic uveal melanoma
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Case Series</th>
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<tr>
<td>Number of patients</td>
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<td>Outcomes recorded</td>
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Initial stage was 10 pts, if at least 2 non-progression then to continue to stage 2, but study stopped after stage 1.

**Results**

5 pts experienced 8 grade 3/4 toxicity
Only 1 of 10 achieved SD at 3 months. (initially 13 pts entered but 3 discontinued due to rapid DP)

**Additional comments on quality of study**

Phase II multicentre (6), non-randomised trial.

1 CR, 3 PR, PFS 28.5weeks, OS 61weeks

**Additional comments on quality of study**

multisite series from 7 centres
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<tr>
<td>Case Series</td>
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<td>Systemic therapy in MUM: second line,</td>
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<tr>
<td>Case Series</td>
<td>19pts</td>
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**Results**

No response

**Applicable?**

**Conclusions**

Additional comments on quality of study

single centre series
Transarterial chemoembolization of liver metastases from uveal melanoma after failure of systemic therapy: toxicity and outcome


Study Type: Case Series

Number of patients: n = 25,

Study aim/Intervention: TACE after failure of systemic treatment,

Comparators: Response evaluated by 2 experienced radiologist with a 3rd if disagreement

Follow-up: No reported grade 4 toxicity, 6 events of grade 3 PR and SD at 2 months in 14 pts (2-9 months)

Outcomes recorded: No significant difference between cisplatin + fotemustine group 2 had extrahepatic progression

1yr survival 15%

Survival longer if pre-treatment LDH was low.

Additional comments on quality of study: retrospective

Aflibercept (VEGF Trap) in inoperable stage III or stage IV melanoma of cutaneous or uveal origin


Study Type: Case Series

Number of patients: n = 25,

Study aim/Intervention: Aflibercept (VEGF Trap) in inoperable stage III or stage IV melanoma of cutaneous or uveal origin

Comparators: Response evaluated by 2 experienced radiologist with a 3rd if disagreement

Follow-up: No reported grade 4 toxicity, 6 events of grade 3 PR and SD at 2 months in 14 pts (2-9 months)

Outcomes recorded: No significant difference between cisplatin + fotemustine group 2 had extrahepatic progression

1yr survival 15%

Survival longer if pre-treatment LDH was low.

Conclusions
### Study Type
- Case Series

### Number of patients
- 9 patients of novel therapy.

### Patient Characteristics

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### Study aim/Intervention
- single arm phase II trial

### Comparators

### Follow-up
- The study provides 4-month PFS data (56%) in the setting of a well-conducted clinical trial in metastatic disease

### Outcomes recorded

### Results

### Applicable?
- no

### Conclusions

### Additional comments on quality of study

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**Study Type** | **Case Series**
---|---
**Number of patients** | 9 patients of novel therapy.
**Patient Characteristics** | Inclusion/Exclusion
**Study aim/Intervention** | single arm phase II trial
**Comparators** |  
**Follow-up** | The study provides 4-month PFS data (56%) in the setting of a well-conducted clinical trial in metastatic disease
**Outcomes recorded** |  
**Results** |  
**Applicable?** | no
**Conclusions** |  
**Additional comments on quality of study** |  

Q4. What is the optimal treatment for oligometastatic disease outside the liver

Grading: 3  Non-analytic studies (for example, case reports, case series)

8902  Total pancreatectomy for metastatic melanoma: Is it worth it?  2012
Roch AMD, Vychnevskai K, Lermite E, Arnaud J, HPB, Conference

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Results

Applicable?  Yes

- 62-year old woman with isolated pancreatic metastases from a choroidal malignant melanoma (CM).
  CM was treated with enucleation 4 years before.

- PT UNDERWENT TOTAL PANCREATECTOMY with spleen preservation.
- Preop imaging = no peritoneal seeding or other sites of metastatic disease; no other metastatic foci in abdomen at laparotomy.
- 13 secondary melanoma deposits and clear excision margins (final histological examination).

RESULTS:
- Pt remained disease-free 22 months later.
- Only complete surgical resection of limited pancreatic metastases seems to be associated with improved overall and disease-free survival.

CONCLUSION: Despite the significant mortality and morbidity of total pancreatectomy, we advocate reconsidering this kind of aggressive surgery as a curative treatment option in selected patients for pancreatic melanoma metastases with disease spread over the whole gland

Additional comments on quality of study  CASE STUDY - thus very low quality