Article:
Fingret, J., Sisley, K., Valluru, M.K. et al. (2026) Surgical interventions improve survival in patients with metastatic uveal melanoma. Clinical Surgical Oncology, 5 (2). 100102. ISSN: 2773-160X

https://doi.org/10.1016/j.cson.2025.100102

Clinical Surgical Oncology 5 (2026) 100102

Contents lists available at ScienceDirect

Clinical Surgical Oncology

journal homepage: www.journals.elsevier.com/clinical-surgical-oncology

Original Article

Surgical interventions improve survival in patients with metastatic uveal melanoma

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ARTICLE INFO

Keywords:
Adult ocular tumours
Choroidal melanoma
Liver metastasis
Irradiation
Uveal melanoma

ABSTRACT

Background: Metastatic uveal melanoma (UM) has a poor prognosis. UM predominately metastasizes to the liver. Surgical treatment of liver metastasis from uveal melanoma (LMUM) remains controversial. We evaluated the survival of LMUM patients treated with different primary (enucleation, proton beam, Ruthenium plaque, stereotactic radiosurgery and metastatic surgical interventions (resection ± radiofrequency ablation – RFA) compared with chemotherapy alone or no treatment.

Methods: 100 LMUM patients were studied. 33 had surgical interventions, 46 had chemotherapy alone and 21 had no treatment. Mean survival time was analysed for each primary and metastatic treatment group. The overall difference in survival times from primary diagnosis and metastatic diagnosis was analysed using chi-squared and log rank tests.

Results: Mean survival times (months) since metastatic diagnosis for the surgery group (40.088) and RFA + surgery group (34.010) were significantly longer than the chemotherapy group (21.631) and the no treatment group (8.325); $p<0.001$. Time interval differences between primary and metastatic diagnoses were not significant between secondary metastatic treatment groups but were significant between primary treatment groups ($p=0.003$): multiple primary treatments and ruthenium plaque had the longest intervals.

Conclusion: This retrospective study highlights how survival can be improved by surgical management of LMUM patients in selected cases.

1. Introduction

Uveal melanoma (UM) is a rare cancer of the uvea, comprising the iris, ciliary body, and choroid with an incidence of 2–8 per million (Jager et al., 2020). UM arises from uveal melanocytes. The 5- and 10-year metastasis rates are 25 % and 34 % respectively (Diener-West et al., 2005a). Metastasis occurs most frequently to the liver and is associated with poor prognosis and metastatic death. Factors linked to metastasis and worse outcomes include large primary tumour size, epithelioid cell type and ciliary body involvement (Jager et al., 2020), monosomy 3 (M3), increased copy numbers of chromosome 8 (Sisley et al., 1992; Prescher et al., 1996) and BRCA1-associated protein 1 (BAP1) inactivation (Jager et al., 2020).

When primary UM metastasizes, it spreads exclusively to liver in 50 % of cases. UM metastasizing to the liver follows two discrete patterns: a miliary disease pattern, whereby innumerable tiny metastases are visible throughout the liver and a nodular disease pattern, whereby there are larger and discrete metastases (Yavuzyigitoglu et al., 2021). Prognosis of UM patients with liver metastases is dismal, irrespective to treatment method. Mortality rate is 80 % after 1 year, 92 % after 2 years and only 1 % of patients survive after 5 years (Yavuzyigitoglu et al., 2021; Diener-West et al., 2005b).

In terms of treatment, most systemic chemotherapy does not improve survival for liver metastases from UM (LMUM) (Khoja et al., 2019a; Rantala et al., 2019; Rodriguez-Vidal et al., 2020), but for a subgroup of UM patients improved survival has been noted. Surgical treatment options for metastatic disease can be considered if the patient has no extrahepatic disease and the pattern of spread is nodular. There is merit in treating liver involvement with liver directed therapies. These include surgical resection, radiofrequency/thermal ablation (RFA), whole liver

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https://doi.org/10.1016/j.cson.2025.100102
Received 7 March 2025; Received in revised form 11 October 2025; Accepted 27 October 2025
Available online 30 October 2025

cytotoxic perfusion and others (Kaštelan et al., 2022; Rowcroft et al., 2020). Surgical resection is reserved for patients who are fit enough to tolerate general anaesthesia. When microscopically complete resection (R0) is achieved, there is a 27-month survival, compared to 11–14 month overall survival (OS) without R0. However, local relapse is common. Less than 10 % of LMUM patients are suitable for resection due to hepatic disease diffusion (Hand et al., 2020; Gomez et al., 2014).

RFA is an alternative for poor surgical candidates with a small number of lesions. It increases the rate of R0 resection, is effective in primary or secondary liver tumours and has a low morbidity and mortality (Liu et al., 2014). Mariani et al. (2016) studied 72 patients with R0 LMUM and showed that RFA can be used to treat LMUM and spare hepatic parenchyma. They compared OS and disease free survival (DFS) of patients treated by RFA ± surgical resection versus surgical resection alone (S). The OS in the RFA group was 28 months and 27 months in the S group. The DFS was 7 and 10 months respectively. These differences were not statistically significant (Mariani et al., 2016). Other research groups also found no differences in OS and DFS between RFA and surgery for LMUM (Bale et al., 2016; Putzer et al., 2019).

The purpose of this study is to further investigate the usefulness of surgical resection and/or radiofrequency ablation in the treatment of metastatic UM.

2. Materials and methods

2.1. Recruitment

Patients who were treated with LMUM at the National Sheffield Ocular Oncology Service (SOOS), Royal Hallamshire Hospital, Sheffield, UK between 1996 and 2016 were identified from a secure database. At our centre, all patients with UM are recruited in a surveillance program, whereby after a diagnosis of primary UM, six-monthly ultrasound scans of the liver are arranged for 5 years and then yearly afterwards. If any abnormalities are found, patients have magnetic resonance imaging (MRI) of the liver for radiological confirmation of liver metastasis. In these patients with MRI evidence of liver metastasis, a staging computerised tomography (CT) scan of the thorax, abdomen and pelvis is arranged to assess for extra-hepatic disease and staging of disease. All patients are referred to a dedicated hepatobiliary team comprising a surgeon, radiologist and clinical nurse specialist.

2.2. Definitions and inclusion criteria

We used the following definition:

- Miliary disease: >10 metastases in ≥6 liver lobes, with ≥4 lesions of >3 cm size
- Nodular disease: ≤10 metastases in ≤5 liver lobes, with ≤3 lesions of ≤3 cm size

Surgical resection was offered to patients whose metastatic disease could be resected in a single stage with potentially curative intent leaving a future liver remnant (FLR) of at least 35 %.

Ablation (Radiofrequency or Microwave) was offered to patients who could not be offered potentially curative liver resection but had a low tumour burden which could be completely ablated either percutaneously or laparoscopically. All patients offered surgery or ablation had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with extrahepatic disease or a poor performance status were not offered surgical intervention.

2.3. Interventions

UM patients received treatment for their primary tumours by one of the following modalities: globe saving treatments such as ruthenium plaque brachytherapy, stereotactic radiosurgery, proton-beam therapy, rarely local resection, or if the globe cannot be saved or if patient choice, enucleation surgery was performed. In the rare instance that any of the globe saving treatments failed, a second treatment, often enucleation surgery, was performed.

All patients identified with metastasis at surveillance were discussed at the ocular oncology MDT which has input from the medical oncology as well as hepatobiliary teams.

In patients with miliary pattern hepatic disease or extra-hepatic disease, patients were referred to the medical oncology team for systemic chemotherapy/immunotherapy. Liver biopsy was performed in these patients by the hepato-pancreatico-biliary (HPB) department if this was to help target treatment.

In patients with nodular hepatic disease without extrahepatic involvement, patients were referred to and assessed by Mr Ali Majeed at the HPB department (Northern General Hospital, Sheffield) for the most appropriate surgical intervention. Surgical resection was offered to patients with unilobar nodular peripheral metastases. RFA was offered to patients whose metastatic tumours in the liver could be completely ablated in a single stage. This was performed either percutaneously or laparoscopically. Patients were regularly followed up as per departmental standard operating policy and meticulous records were maintained at SOOS and HPB departments as far as possible.

2.4. Data collection and variables

A retrospective cohort analysis identified patient age at diagnosis, sex, primary UM treatment, interval to liver metastasis, type of metastasis, treatment of metastatic disease, post-operative course, date of last follow up and date of death. Genetic data was available for certain patients who had specimens taken at primary treatment. Overall survival was measured: This was defined as the time between primary UM treatment and death from any cause and the time between metastatic UM treatment and death from any cause. Data was recorded on an Excel spreadsheet, which was encrypted and stored on a secure, password protected NHS computer. No specific funding was obtained for this study.

2.5. Statistical analysis

Data are presented as mean values or numbers of patients. Statistical analysis was performed on Microsoft Excel, IBM SPSS Statistics 25.0 and RStudio (https://github.com/JoachimGoedhart/PlotsOfDifferences). The differences between metastatic treatment groups (surgical resection, RFA, chemotherapy and no intervention), primary treatment groups and genetic outcome categories were estimated with the Chi-square test. Patient survival distributions were estimated by Kaplan-Meier using the log-rank test. Cox proportional hazards regression was performed to evaluate the independent effect of RFA ± surgery The linear predictor score (X β) was calculated, and the difference in X β between other groups and the combined RFA/surgery group was assessed. Statistical significance was evaluated using ANOVA and a two-tailed *t*-test. Differences were considered significant if the p-value was <0.05.

2.6. Statement of ethics

This study gained Research and Development approval from Sheffield Teaching Hospitals Ethics committee (Approval No: STH18697). Informed consent from patients to participate in this study was not required because this was a retrospective analysis of treatment outcomes. This was not a clinical study, so patients were not randomised to treatment arms. Ethical approval was given to study the data for analysis to identify outcomes of surgery versus other treatment regimes.

3. Results

There was data for a total of 100 patients with LMUM: 20 patients had liver resection (S); 13 patients had radiofrequency ablation with liver resection (RFA + S); 46 patients had chemotherapy alone and 21 patients had no treatment for metastatic disease. There was data available regarding primary treatment for 87 of these patients. The number of patients where data is available is signified by (n) for each variable. Table 1 indicates that there was a significant difference between primary treatment and mean age: mean age was lower for RFA + S patients. 30 cases had available genetic data. There was no significant difference between genetic groups. Patients with the worst genetic prognosis (M3 + 8q gain) were mainly in the chemotherapy and no treatment groups.

Patients treated with RFA ± S had significantly longer OS times since metastatic presentation compared to chemotherapy or no treatment ($p < 0.001$). Estimated mean survival times in months since metastatic diagnosis for the different liver metastases treatment groups are as follows: surgery 40.9 months; RFA + S 34.0 months; chemotherapy 21.6 months and no treatment 8.3 months (Fig. 1, Table 2). However, there was no significant difference in OS from metastatic diagnosis between different primary treatment groups ($p = 0.83$, Supplementary Fig. 5). There was no significant difference in the survival from primary diagnosis between metastatic treatment groups ($p = 0.083$, Supplementary Fig. 1), or between primary treatment groups ($p = 0.119$, Supplementary Fig. 4). Table 1 lists all cases in the no-treatment group (n = 21). For one case, the dates of secondary liver metastasis and its treatment are unavailable (primary, referral, and treatment dates are recorded for OS analysis), so this case was excluded from the Kaplan–Meier analysis, resulting in n = 20 for the no-treatment group.

There was no significant difference in the time interval between primary and metastatic diagnosis between the metastatic treatment groups ($p = 0.610$, Fig. 2). The difference in time intervals between primary and metastatic diagnoses was significant between primary treatment groups ($p = 0.003$, Fig. 3, Table 3), with ruthenium plaque having the longest mean interval times in months (65.113). This was followed by stereotactic radiotherapy (53.174), then enucleation (37.126) and proton-beam therapy with the shortest mean interval time at 29.832 months.

Cox regression analysis confirms the independent benefit of RFA ± surgery for age/gender variables. The results are presented as X β linear predictor score in supplementary material (Supplementary Figs. 7 and 8). The regression analysis where genetic data was available (n = 30) does not show an independent benefit of surgery. However, genetic information was only available for patients undergoing enucleation surgery. Classically, enucleation is reserved for larger primary tumour and this will skew the data.

All data figures and tables are available in the supplementary material provided. The large variability in the surgery arm is caused by a few long-term survivors. There were no deaths or significant morbidity in patients undergoing surgery or ablation. One patient who had a 3cm metastasis ablated formed an abscess at the ablation site 6 weeks postoperatively and was treated with percutaneous drainage with a satisfactory outcome.

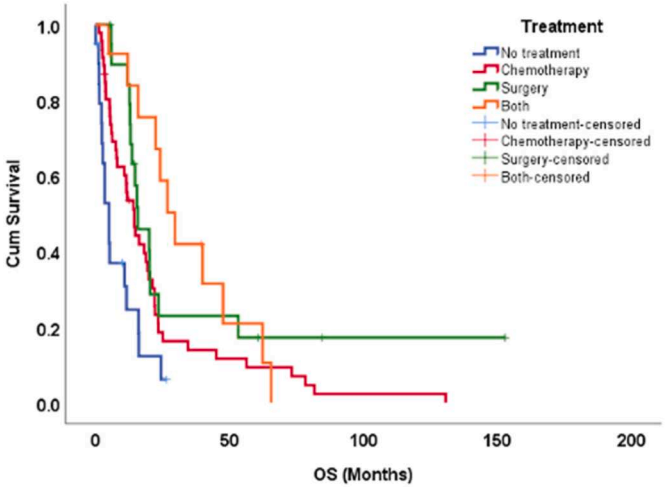

Fig. 1. Overall survival in months from secondary diagnosis between secondary liver metastasis treatment groups *($p < 0.001$)*.

Table 2
Mean survival in months (with standard error) since secondary diagnosis between secondary liver metastasis treatment groups.

Treatment	N	Mean Survival (months)	Standard Error (SE)
No treatment	**20**	**8.325**	**1.887**
Chemotherapy	**46**	**21.631**	**3.955**
Surgery	**20**	**40.888**	**12.358**
RFA + Surgery	**13**	**34.010**	**5.982**
Overall	**99**	**24.626**	**3.374**

Table 1
Patient demographic and clinical features of the liver metastases from uveal melanoma (LMUM) treatment groups. N signifies the number of patients where data was available. Standard deviation (SD) is given for means.

Variable	No. of patients				
	S (n)	RFA + S (n)	Chemotherapy (n)	No Treatment (n)	*p* value
Sex ratio (male, female)	13, 7 (20)	6, 7 (13)	26, 20 (46)	10, 11 (21)	0.632
Age in years (Mean ± standard deviation [SD])	63.8 ± 12 (19)	55 ± 10.34 (13)	61.52 ± 12.19 (45)	67.82 ± 10.61 (20)	**0.021**
Treatment of primary (n)	(18)	(13)	(37)	(19)	
Proton beam radiotherapy	1	2	5	0	0.815
Enucleation	9	5	21	11	
Ruthenium plaque	5	4	6	3	
Stereotactic radiosurgery	2	1	2	2	
Multiple	1	1	3	3	
Mean time from treatment of primary tumour to liver metastasis in months (Mean ± SD)	58.64 ± 50.66 (20)	30.27 ± 31.61 (13)	40.16 ± 42.54 (46)	39.96 ± 31.11 (20)	0.223
Chromosome abnormality (n = 30)					
Monosomy 3 (M3) (n = 5)	2	0	2	1	0.835
8q gain (n = 2)	1	0	1	0	
M3 + 8q (n = 18)	2	2	8	6	
None (n = 5)	1	0	2	2	

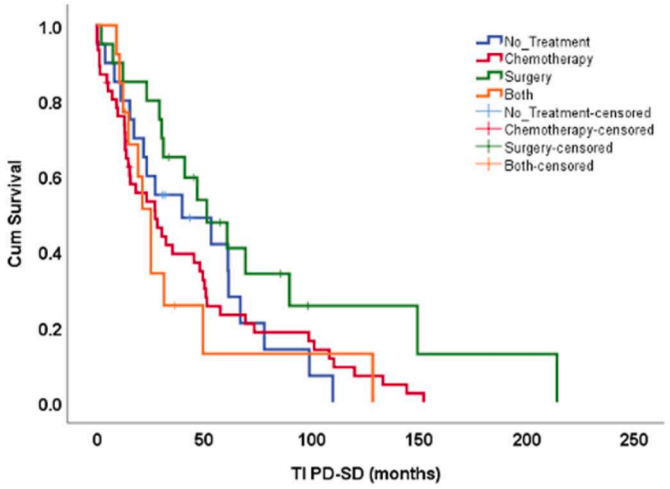

Fig. 2. Time interval between primary and metastatic diagnoses between secondary treatment groups *(p=0.610)*.

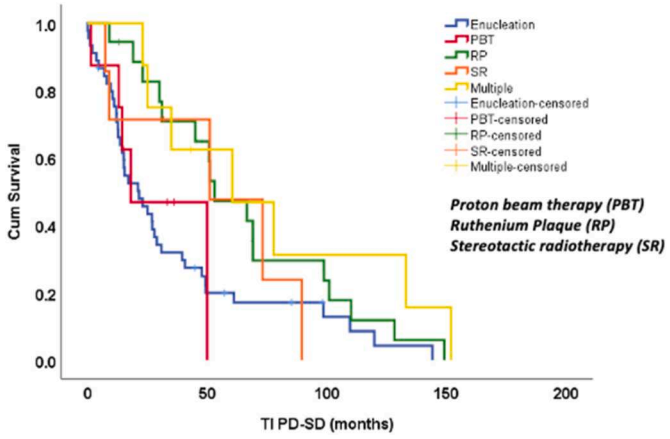

Fig. 3. Time interval between primary diagnosis and metastatic diagnosis between primary treatment groups *(p=0.003)*.

4. Discussion

This retrospective study showed that surgical interventions (RFA ± surgical resection) improve the survival of LMUM comparted to when patients are treated with chemotherapy or no treatment. This is supported by the literature (Hand et al., 2020; Gomez et al., 2014; Liu et al., 2014; Mariani et al., 2016; Bale et al., 2016; Putzer et al., 2019).

UM is a rare tumour and when metastasis occurs, effective treatments are limited, with no current standard of care (Diener-West et al., 2005; Carvajal et al., 2017). Dacarbazine is a chemotherapeutic option used for cutaneous melanoma and has been used for UM. It has not shown to significantly affect survival (Sacco et al., 2013). Other chemotherapy regimens have been used but with disappointing results: cisplatin, sunitinib, vinblastine, gemcitabine, treosulfan, fotemustine and various combinations of these (Sacco et al., 2013; Schinzari et al., 2017; Peuker et al., 2018; Piperno-Neumann et al., 2017). Immune checkpoint inhibitors have been studied in metastatic UM. Ipilimumab is a human monoclonal antibody, which blocks the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and is approved for the treatment of unresectable cutaneous melanoma but authors concluded it has minimal activity (Heppt et al., 2017). Ipilimumab has better results when combined with PD-1 inhibitor, nivolumumab (Pelster et al., 2021). Tebentafusp is a bispecific protein, which has higher 1-year OS rates than other immunotherapies. It consists of an affinity-enhanced T cell receptor fused to an anti-CD3 effector. This receptor binds to gp100 antigens on UM cells. However, it must be noted that tebentafusp only has activity in patients with the HLA-A*02:01 genotype and is not NICE approved (Sacco et al., 2020; Nathan et al., 2021). Systemic therapies are an evolving landscape and studies have shown promising results when combining liver directed treatments with immunotherapy (Nazarova et al., 2025; Blomen et al., 2021). Two large prospective studies (Koch et al., 2021; Carvajal et al., 2022) analysed overall survival when treating metastatic uveal melanoma with immune checkpoint inhibitors and tebentafusp respectively. Although these studies have a larger sample size (178 and 127), OS was considerably lower than those receiving liver directed therapies in our study: 16 months compared with 40.9 (surgery) and 34 (RFA + surgery) months. These treatments were also associated with a higher proportion of adverse events. A comparison should be made with caution however: these studies included patients with extra-hepatic metastases.

Liver resection has shown improved survival data compared to chemotherapy but is not curative by any means (Hand et al., 2020; Putzer et al., 2019). This is reflected in our study. Surgery or ablation to resect or ablate UM liver metastases inherently introduces a selection bias because these patients will have to be fit for intervention and have a low tumour burden. There is preliminary data suggesting benefits to patient outcomes following hepatic intra-arterial chemotherapy, radio-embolization and hepatic chemoembolization. Chemosaturation with percutaneous hepatic perfusion surgically isolates the afferent blood supply to the liver, which allows high-dose chemotherapy (melphalan) to be directly delivered to the organ. The uveal melanoma UK national guidelines advise liver resection may be associated with longer survival (Carter et al., 2025). Our study contributes to this finding, by offering one of the largest single-centre series reported on this topic.

Metastases occur to the liver primarily, but also to the lungs, bone, skin and brain. The metastatic process has three components: primary tumour, haematopoetic tissue and liver (Jager et al., 2020). From the primary tumour, UM cells enter systemic blood circulation and pass through the right side of the heart, lungs, left side of the heart, aorta, and liver. The cells then pass into haematopoietic tissue, including bone marrow and spleen (Eide et al., 2013).

Table 3
Mean and median time interval in months between primary diagnosis and metastatic diagnosis between primary treatment groups, with standard error and 95 % confidence intervals *(p=0.003)*.

	Mean[a]				Median			
			95 % Confidence Interval				95 % Confidence Interval	
Primary treatment	Estimate	Standard error	Lower Bound	Upper Bound	Estimate	Standard error	Lower Bound	Upper Bound
Enucleation	37.126	6.254	24.867	49.385	21.530	5.448	10.852	32.208
Proton beam therapy	29.832	7.990	14.171	45.492	17.980	10.597	0.000	38.751
Ruthenium plaque	65.113	9.723	46.056	84.169	53.060	10.901	31.694	74.426
Stereotactic radiosurgery	53.174	14.061	25.615	80.733	50.990	30.329	0.000	110.436
Multiple treatments	76.499	19.308	38.655	114.344	60.420	25.504	10.432	110.408
Overall	48.276	4.882	38.707	57.846	30.830	6.662	17.773	43.887

[a] Estimation is limited to the largest survival time, if it is censored.

UM infiltrates liver parenchyma with periportal localisation and exhibits angiogenesis, which is necessary for tumour growth. Jager et al. (2020) hypothesized that the balance of two molecules plays a part in metastatic growth: vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) (Jager et al., 2020). Hepatic stellate cells produce hypoxia-induced collagen and infiltrating UM cells produce hypoxia-induced VEGF. This is countered by PEDF, which is produced by hepatic stellate cells. However, platelet-derived growth factor and transforming growth factor-b produced by UM cells block PEDF production (Nwani et al., 2016). Once there is more VEGF than PEDF, metastatic growth may occur (Jager et al., 2020).

The growth pattern and spread of metastases within the liver has implications on prognosis. Liver metastasis growth patterns are described as "replacement" or "desmoplastic" (Barnhill et al., 2022). The replacement histopathologic growth pattern (rHGP) is defined by tumour cells that infiltrate and replace hepatocytes at the peritumoural-stromal interface along abluminal surfaces of sinusoidal vessels or venules of the portal tracts, and allows migration, along vessels of the tumour (Latacz et al., 2020). Desmoplastic HGP (dHGP) is defined by a distinct separation between metastasis from liver parenchyma by an annulus of desmoplastic fibrous tissue. These two patterns denote important differences in prognosis: Colorectal carcinoma metastases with rHGP were associated with a poor prognosis and those exhibiting dHGP had a more favourable prognosis. LMUM predominately exhibits rHGP, and this has a significant adverse effect on prognosis (Barnhill et al., 2020).

These factors impact how healthy liver parenchyma is replaced by tumour cells. Having a higher proportion of liver parenchyma replaced by LMUM (larger tumours and more LMUM metastases) is associated with reduced OS and progression free survival (Khoja et al., 2019b). Therefore, there is a rationale to reduce the tumour bulk through surgical resection and other liver-directed therapies. Tumours which occupy a relatively larger liver volume can still be resected, because of the organ's unique ability to regenerate.

There was no difference in OS between different primary treatment groups, as previously found. The ruthenium plaque group had a longer time to metastasis. This may be because this treatment is often used for smaller tumours (Papageorgiou et al., 2011). However, recent work has shown no difference in metastasis rate between smaller and larger UM treated with Ru106 (Mirshahi et al., 2022).

Our study demonstrates a longer mean survival when patients were treated with either surgical resection alone, or in combination with RFA, compared to treatment with chemotherapy alone or no treatment. We have also demonstrated that larger tumours which require enucleation have a higher risk of metastasis and had a shorter interval to metastasis (compared to Ru106) but interestingly had the same survival as the globe saving group.

It is important to note that only patients with nodular metastases were suitable for surgery. Patients with more advanced disease and more extensive metastases may not be deemed suitable for surgery. Any attempted curative operation would be futile. Patients who opted for chemotherapy, or no treatment, may not have been fit enough for surgery. They may have a decreased physiological reserve and therefore, a worse prognosis. Additionally, the retrospective study design means that treatment allocation was not randomised. These factors mean that selection bias is inherently introduced.

Our cohort's data spans between 1996 and 2016 and BAP1 inactivation's relationship with metastatic uveal melanoma was first published in 2010 (Harbour et al., 2010). Hence, we do not have this data for comparison in this series.

Regression analysis involving the whole series with age and gender shows an independent benefit of surgical treatment. Where genetic information was available, patients underwent enucleation for primary tumour surgery and larger tumours tend to be treated in this manner (Table 1, n = 30). Patients with the worst genetic prognostic indicators (M3 + 8q gain in combination) (Sisley et al., 1992; Prescher et al., 1996) fell into the chemotherapy and no treatment groups. The RFA/surgery groups had fewer patients where genetic information was available, potentially skewing the results. We did not have available data on largest basal tumour diameter, number of liver metastases and synchronous versus metachronous disease and appreciate that these are limitations of the study.

Furthermore, this was not a randomised prospective study and prospective validation is warranted. Despite these limitations, we have evidence of improved survival in LMUM patients who were treated with surgical interventions. This supports the literature that a reduced tumour bulk proportion in the liver is significant in improving survival. Further studies are required in this field to yield more evidence on the use of surgical interventions in treating uveal melanoma liver metastases. We conclude that in selected patients with nodular type liver involvement, surgical resection and/or RFA was associated with prolonged survival compared with historical non-surgical approaches. UM is a rare malignancy and approximately half these patients go on to develop liver metastases. Large multicentre collaborations are required to achieve adequate power for future validation.

CRediT authorship contribution statement

Jacob Fingret: Writing – original draft. **Karen Sisley:** Writing – review & editing, Supervision, Resources. **Manoj K. Valluru:** Formal analysis. **Ian Rennie:** Writing – review & editing, Conceptualization. **Sachin M. Salvi:** Writing – review & editing, Supervision, Conceptualization. **Heather Allen:** Investigation, Formal analysis. **Ali Majeed:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Funding sources

The Justham Alumni scholarship award supported MKV.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cson.2025.100102.

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