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ORIGINAL ARTICLE

Metastatic uveal melanoma: A valid indication for liver resection

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Summary

Purpose: *Owing to its relative resistance to chemotherapeutics, prognosis following the diagnosis of metastatic uveal melanoma has remained disappointing. On this basis, liver resection in cases of isolated hepatic metastases has been postulated as a viable treatment option. Herein we performed an analysis of patients who underwent hepatic metastatectomy for uveal melanoma and compared their outcomes to those undergoing resection for colorectal cancer liver metastases (CRLM) in the same time period.*

Methods: *From 2008 to 2018, all patients referred to our unit with hepatic metastases were included for analysis. Performing a 3:1 matched cohort analysis, patients with metastatic uveal melanoma were matched for age, sex, operative approach, tumour number and size to those undergoing resection for CRLM. Clinicopathological data was sought from a prospectively maintained database and reviewed along with 30-day post-operative morbidity and mortality.*

Results: *Fifteen patients underwent hepatic metastasectomy for primary uveal melanoma. A further 45 patients undergoing hepatectomy for metastatic colorectal cancer acted as the control group. No in-hospital mortality was noted with four patients (26.6%) developing post-operative morbidity. The median follow-up period following melanoma resection was 27 months (range 5-211) with 1-, 3- and 5- year overall survival for this cohort of 86.6%, 53.3% and 40%, respectively. There was no difference in overall survival between the melanoma and CRLM group (p =0.80).*

Conclusion: *In patients presenting with hepatic metastases from uveal melanoma, this present study supports the rationale to proceed to surgery with acceptable morbidity and mortality.*

Key words: *liver metastases, metastatic uveal melanoma, metastasectomy*

Introduction

Despite representing the most common primary intraocular malignancy in adults, uveal melanoma remains an unusual entity with an incidence of about 5 per million persons per year. Biologically distinct from the cutaneous subtype, uveal melanoma arises from melanocytes in the iris, ciliary body or choroid [1]. Surgical enucleation and targeted radiotherapy form the mainstay of treatment [2,3] with 50% of patients developing metastatic disease. In contrast to cutaneous melanoma which primarily metastasises to soft tissue and lymphatics, uveal melanoma disseminates almost exclusively to the liver requiring systemic therapy [4].

Owing to its relative rarity and resistance to traditional chemotherapeutics, metastatic uveal melanoma continues to have a poor prognosis. Sensitivity to traditional chemotherapy is poor with just 4.6% of patients demonstrating a sustained response [5]. While improved progression

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free survival was shown following treatment with selumetinib, (a MEK 1/2 inhibitor), this improvement was not borne out on survival analysis [6] and adverse events amongst patients was common. Ipilimumab has also been trialled, unfortunately demonstrating disappointing results with less than 5% of patients showing a reduction in tumour size [7].

Hepatic metastatectomy is now standard of care for a number of malignancies. In the setting of colorectal cancer liver metastases, metastatectomy is associated with acceptably low perioperative risk [10], and a median postoperative survival approaching 5 years, compared to 24 months when chemotherapy is given alone [11]. While a number of groups have proposed liver resection in the setting of metastatic uveal melanoma [8,9] acceptance of this approach has been hampered by the lack of strong data to illustrate the safety of metastectomy for this indication. Herein we present our single centre experience of hepatic metastatectomy for metastatic uveal melanoma, comparing perioperative variables and postoperative outcomes to a cohort of patients undergoing metastatectomy for colorectal liver metastases.

Methods

Data was interrogated for all patients undergoing hepatic metastatectomy for melanoma metastases from January 2008 to January 2018 at the department of surgery, St. Vincent's University Hospital, Dublin. Perioperative and clinicopathological details were sought from a prospectively maintained database. The selection criteria employed for metastatectomy included evaluation of the lesions with high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) to determine the probability of achieving an R0 resection. All potential cases were reviewed at a multi-disciplinary team conference, attended by medical oncologists, radiologists, pathologists and hepatobiliary surgeons.

Operative details, 30-day morbidity and mortality and overall survival were analysed for all patients who underwent hepatic metastatectomy for metastatic melanoma. These were then compared to outcomes for patients undergoing resection for colorectal liver metastases. Each metastatic melanoma patient was matched by a 3:1 ratio to patients undergoing hepatic resection for colorectal liver metastases according to age, sex, number of metastases and segment resected. This study was approved by the ethics committee of St. Vincent's University Hospital.

Statistics

Overall survival in both groups were assessed by Kaplan-Meier method and log rank test. Continuous variables were expressed as means (±SEM) and compared between subgroups when appropriate using the Mann-Whitney U-test. A p value of less than 0.05 was considered to be significant. Statistical analysis was performed using computer software GraphPad Prism version 6.0 for Mac, GraphPad Software, La Jolla California USA (www.graphpad.com).

Results

Fifteen patients underwent hepatectomy for metastatic uveal melanoma. The median patient age was 65 years, the majority of the cohort were female. A number of different operative approaches were undertaken depending on the size and

Table 1. Demographic details, intraoperative details and oncologic results

Patient variables	*Uveal Melanoma metastases (n=15)*	*Colorectal metastases (n=45)*	*p value*
Patients			
Sex M,F	5, 10	15, 30	-
Median Age (range)	65 years (21-67)	64.5 years (27-72)	-
Operative Approach			
Right Hepatectomy	5	15	-
Left Hepatectomy	1	3	-
Left lateral Sectionectomy	4	12	-
Segmentectomy	5	15	-
Intraoperative details			
Duration of Surgery	181.8 ± 20.14	224.4 ± 12.52	0.072
Blood Loss (mls)	772.6 ± 266.2	1103 ± 169.2	0.29
Transfusion, n (%)	3 (20)	7 (15.5)	0.61
Oncologic results			
Maximum tumour size, mm	40.13 ± 6.28	42.79 ± 4.79	0.75
Number of lesions	1.53 ± 0.19	2.3 ± 0.29	0.10
Operative margin R0, R1	15, 0	40, 5	0.13

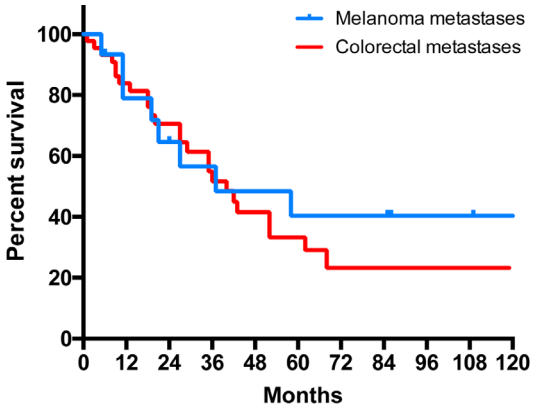
Table 2. Postoperative morbidity and mortality

	Uveal Melanoma metastases (n=15)	*Colorectal metastases (n=45)*
30 day mortality, n (%)	0	0
Liver Specific Morbidity, n (%)	1	0
Clavien Dindo Grade 1	0	2
Clavien Dindo Grade 2	3 (20)	8 (18)
Clavien Dindo Grade 3	1	0
Clavien Dindo Grade 4	0	0
Median Followup (months)	27	35

location of the tumour including formal right or left lobectomy with segmentectomy reserved for smaller lesions. Maximum tumour size was 40 mm on average with all patients achieving a histological R0 resection margin. A further 45 patients undergoing hepatectomy for metastatic colorectal cancer acted as the control group. As detailed in Table 1, both groups were comparable regarding age, sex, operative approach, tumour number and size. Operative time, blood loss and blood transfusion requirements were equally similar in both groups (Table 1).

Full postoperative outcomes are outlined in Table 2. No in-hospital mortalities were recorded in either cohort. In total, 4 (26.6%) of patients in the metastatic melanoma group developed a postoperative complication. One patient developed a postoperative collection in the resection bed, thus deemed a liver specific morbidity. This necessitated radiological guided drainage by interventional radiology and was classed as a Clavien-Dindo grade 3 complication. Two further patients developed lower respiratory tract infections with a further patient treated for a superficial wound infection. All were successfully managed with antibiotics. In the control group, there were 10 postoperative complications (22.2%). These included 3 wound infections and 5 lower respiratory tract infections, with no significant difference in post-operative morbidity between the two groups (22.2% vs 26.6%).

The median follow-up period following metastatic melanoma resection was 27 months (range 5-211). The median survival following surgical resection of metastatic uveal melanoma was 37 months with 1-, 3- and 5- year survival of 79%, 56% and 40% respectively (Figure 1). The median follow up in the colorectal liver resection group was 35 months (range 1-95). Median survival following liver resection for colorectal liver metastases was 40 months with 1-, 3- and 5- year overall survival of 84%, 64% and 33% respectively. When compared to outcomes following resection for colorectal liver metastases, equivalent survival was shown (p =0.80, Figure 1).



Number of patients at risk				
Month	0	12	36	60
Melanoma metastases	15	13	8	6
Colorectal metastases	45	36	17	10

Figure 1. Kaplan Meier curve showing overall survival of patients following hepatectomy for metastatic uveal melanoma between January 2008 and January 2018. Metastatectomy for uveal melanoma metastases are represented in blue, metastatectomy for colorectal liver metastases are represented in red (p>0.05).

Discussion

Uveal melanoma remains a therapeutic challenge. Despite curative resection with adjuvant radiotherapy, metastatic disease occurs in up to half of the patients, the overwhelming majority affecting the liver [12]. Herein we present our cohort of 15 patients with metastatic uveal melanoma resected at our institution over a 10-year period. Our findings are in keeping with other published series demonstrating a marked survival benefit following hepatectomy for metastatic disease when compared to best chemotherapy alone.

The prognosis for patients diagnosed with metastatic uveal melanoma continues to be guarded. Treatments that have demonstrated efficacy against metastatic cutaneous melanoma have failed to halt disease progression in uveal melanoma patients [13,14]. Immunotherapy has been tried with un-

derwhelming results. Tumour response rates between 5-10% and overall survival of 6.0-9.7 months were seen following treatment with anti-CTLA4 ipilimumab [15-17]. The combination of anti PD-1 nivolumab and pembrolizumab have also been tried in metastatic uveal melanoma but with too little effect [18,19]. However, the mechanism of PD-1 blockade in uveal melanoma is not well described as yet. Unlike cutaneous melanoma, BRAF mutations targeted in current therapies are not typically found in uveal melanoma. This difficulty in obtaining any meaningful improvement in outcomes has led some groups to suggest metastatectomy as a means to prolong patient survival.

A published series from Liverpool describing 17 patients who underwent hepatectomy for metastatic uveal melanoma showed encouraging results with a median overall survival of 27 months [20]. Similarly, Frenkel et al reported a median overall survival of 23 months in 35 patients that underwent hepatectomy from their cohort [21]. Due to lack of effective chemotherapeutic regimens, achieving an R0 resection margin is key to prolonged postoperative survival. The 16-year experience published from the Institut Curie claimed that surgical resection of liver metastases almost doubled their patient survival [22]. Their analysis identified 255 patients who underwent liver resection with an overall survival of 14 months, which increased to 27 months when R0 resection was possible. Furthermore, the Liverpool group achieved a median overall survival of 27 months, citing their 88% R0 resection rate as the cause. In comparison to other published studies, the rate of R0 resection was higher at our institution, with all specimen margins clear of disease on histological analysis. Correspondingly, the median overall survival was shown to be longer at 37 months.

Despite a number of published experiences, there remains a paucity of randomised trials to support the feasibility and safety of liver resection for metastatic uveal melanoma. While we acknowledge this is a single centre experience with a small sample size, this present work informs the current treatment algorithm for metastatic uveal melanoma and supports this rare indication for hepatic resection. Of critical importance is the ability to achieve a R0 resection margin as efficacious adjuvant therapies do not exist for this cohort. As such, only patients with potentially R0 resections should be considered for resection. In carefully selected patients, surgical resection of uveal melanoma liver metastases can provide meaningful postoperative outcomes.

Conflict of interests

The authors declare no conflict of interests.

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