Mapping the treatment pathway for metastatic uveal melanoma (mUM) patients in England: *A qualitative pilot study*

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Background

Uveal melanoma (UM) is a rare disease

- Although UM is the most common form of intraocular melanoma, and the second most frequent melanoma after cutaneous melanoma (CM), it is nevertheless a rare disease.
- In Europe, primary UM is reported to annually affect 2 to 8 Caucasians/million population, with a trend of increasing incidence from southern to northern latitudes [3, 4].
- The annual rate of new UM admissions in England is estimated as 1 per 100,000 persons and has remained stable, relative to population growth, over recent decades [5].
- The genetic, histological, cellular and clinical behaviour of UM is significantly different to CM [1] and categorised as a separate condition by European Rarecare and orphanet initiatives [2].

Primary UM patient characteristics

- ~90% of primary UM tumours involve the choroid - the remainder are confined to the iris and ciliary body [3,4,5].
- The average age of diagnosis is ~60 years old, with an equal distribution between genders [4,5].
- Genetic and environmental risk factors for the disease are unclear - although there is a lower incidence of UM in non-Caucasians, and races with brown eyes [4].

Metastatic uveal melanoma (mUM)

- Despite radical intra-ocular intervention(s) to the primary tumour, ~50% of patients develop metastatic disease - predominately in the liver [5].
- Once metastatic disease occurs, patient have limited therapeutic options with poor outcomes [3]. Reported median time-to-progression is 2-3 months and median overall survival is 7-12 months [6].
- The incidence of mUM in the UK is estimated to affect ~150 patients per year [5, 7]

mUM pathway and treatment options

- In 2015, the UK published their first national uveal melanoma guidelines [3], which subsequently received accreditation from the National Institute for Health and Care Excellence (NICE).
- With few therapeutically effective options available for metastatic patients, however, many of the recommendations for mUM treatment are based on expert opinion, often informed from evidence developed in patients with mCM; and/or to for patients to join a clinical trial.
- It is therefore unclear what mUM patients *actually receive* as their standard of care (SoC).

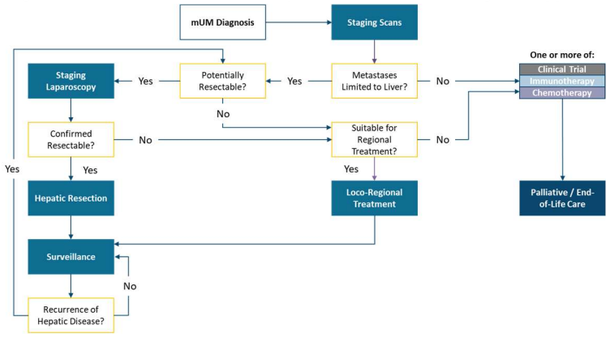
Objectives

- This pilot study aimed to map the real-world pathway for recently diagnosed mUM patients, through qualitatively evaluating their clinical management and treatments received within SoC.

Methods

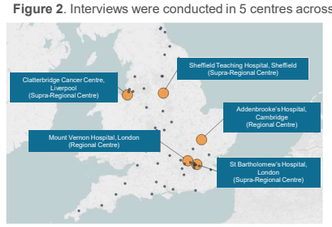
- Based on treatment recommendations within the national guidelines [3], an outline decision-tree for mUM patients was developed (**Figure 1**).

Figure 1. Treatment recommendations for mUM patients based on the UK national guidelines [3]



- On presenting the decision-tree to 5 specialist centres across England (January-June, 2017), 6 senior clinicians were interviewed about their typical: clinical management; medical resource use; treatment decision-making and patient flow(s) between local and regional facilities, when treating mUM patients (**Figure 2**).

Figure 2. Interviews were conducted in 5 centres across England



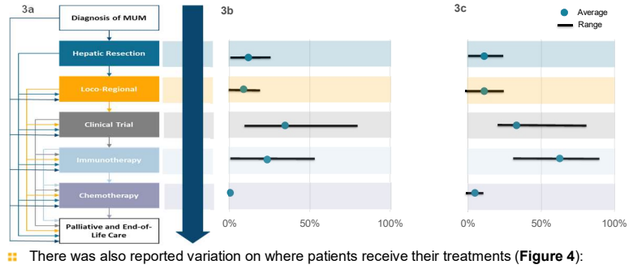
- The interview data were analysed to populate centre-level decision-trees, and then consolidated to inform a consensus SoC pathway.

Notes: A supra-regional centre located in Glasgow, was not part of this initial pilot study.
Orange dots - interviewed centres
Black dots - melanoma treatment centres

Results

- A consensus summary of the treatment hierarchy for mUM patients is depicted in **Figure 3a**.
- There was considerable variation in treatments offered at specialist centres (**Figure 3b & c**)
  - hepatic resection for liver metastases [Mean: first-line 12%; anytime 12%];
  - loco-regional therapies for liver metastases (including percutaneous hepatic perfusion and radiofrequency ablation) [Mean: first-line 7%; anytime 9%];
  - clinical trials (TRAP, SelPac or IMCgp100) [Mean: first-line 37%; anytime 40%];
  - immunotherapy (ipilimumab, pembrolizumab, nivolumab) [Mean: first-line 32%; anytime 62%]
  - chemotherapy (dacarbazine or temozolomide) [Mean: first-line 0%; anytime 9%]
- There was, however, consensus on treatment priorities for mUM patients:
  - If liver metastases were operable then surgical options were considered first;
  - If non-operable, clinical trials were considered, before other therapeutic options.
  - Few patients receive chemotherapies (dacarbazine and/or telozolomide) as a 1st line treatment, or at anytime, unless other treatment options are exhausted, or the patient requests it.
  - All patients were eventually discharged from active treatment to palliative care in the community
- The choice between ipilimumab+/-nivolumab, or pembrolizumab is dynamically influenced by:
  - The latest emergent data;
  - Patient age and underlying comorbidities to tolerate the associated safety profiles of each immunotherapy treatment options;
  - The patient's choice - including practicalities and convenience in adhering to the treatment regimen.

Figure 3. Consensus **(a)** hierarchy and variations in **(b)** first line or **(c)** anytime treatment within the mUM treatment pathway



- There was also reported variation on where patients receive their treatments (**Figure 4**):
  - Hepatic resection: usually performed in centres where a liver multi-disciplinary team (MDT) was available, this may or may not be at the same site as the specialist ocular centre
  - Loco-regional therapies: typically only accessible at a few specialist surgical centres nationally
  - Clinical trials: usually investigational new drugs were initiated and maintained at either supra-regional or regional specialist centres - not all trials were run at all centres and were subject to site selection criteria
  - Immunotherapies: some specialist centres initiated and maintained the treatment in the same centre, while some referred patients to local melanoma centres for the maintenance of the treatment
  - Chemotherapies: administered in general chemotherapy departments across local and regional centres
- There were mixed attitudes as to whether mUM patients could or should receive standard systemic treatments at centres more local to the patient's home.
- The main reason suggested by the specialist oncologists for treatment pathway variations amongst centres, was the absence of effective treatments.
  - Without a proven effective treatment for non-operable mUM patients, many clinicians encourage patients to enrol in trials for new treatments based on the possibility of benefits to extend survival.
  - However, access to centres running therapeutic trials, an availability of open trials, in/exclusion criteria and patient willingness to participate in a trial, limit this as a potential therapeutic option.

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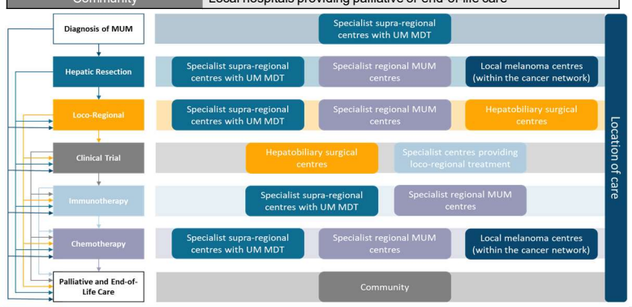
Figure 4. The types of centres of where patients receive treatment

Specialist supra-regional ocular surgical centres with UM multi-disciplinary team (MDT)	•Manage primary UM tumours (staging, ocular radiotherapy/surgery) •Specialise in and lead mUM care - Surveillance and diagnosis - Refer to centres for hepatic surgical options - Clinical trials - Initiate immuno- and chemotherapy
Specialist regional mUM centres	•Deliver UM surveillance •Specialise in mUM care (as above)
Local melanoma centres (within the cancer network)	•Surveillance •Deliver immuno- and chemotherapy
Hepatobiliary surgical centres	mUM staging and hepatic surgical treatment
Specialist centres providing loco-regional treatment	May be specialist regional mUM centres
Community	Local hospitals providing palliative or end-of-life care



Discussion

- The current recommendations for using immunotherapies in mUM patients are based on the approval for use in melanoma generically. At this time, there is limited evidence that the survival benefits observed with these treatments in mCM patients, are similarly conveyed to mUM patients.
- The treatment centres' experience of the disease and their familiarity in using different immunotherapy and chemotherapy agents, contributes to treatment variation in the pathway. This in turn influences the view of clinicians on whether mUM patients could or should receive ongoing standard systemic treatments only at specialist centres or if they could be provided at centres more local to a patient's home.
- 72% of recommendations in the UK guideline are currently based on expert consensus of the Uveal Melanoma Guideline Development Group [3].
  - The development of national / international registries, and other observational datasets of uveal melanoma patients that can pool a collective insight into the clinical, economic and humanistic understanding of the disease pathway, alongside treatment-correlated outcomes could enable greater power to inform decision-making and optimise treatment selection.
  - With the emergence of longer-term patient outcomes data, a more evidence-based approach to informing the guidelines and protocols for managing the mUM pathway will continue to emerge.
- In a recently published quantitative analyses of mUM patients within NHS England medical records [7], a clear trend to earlier and more rapid identification of liver metastases has been observed over the last 5 years. These data highlight the value of introducing national guidelines, implementing surveillance protocols and continued pathway development, so that patients may be treated at an earlier, less advanced stage of their disease.

Conclusion

- The main reason suggested for treatment pathway variations amongst centres, was the absence of effective treatments. Introducing an effective therapeutic option at a defined optimum point in the pathway would be considered a "catalyst to transform the management of care"
- This in turn would lend itself to greater consistency of practice, harmonise care pathways and ultimately improve overall outcomes for mUM patients.

References and Acknowledgments

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