A real world evidence (RWE) approach to characterising an (ultra) rare disease cohort of metastatic uveal melanoma (mUM) patients within National Health Service England (NHSE)

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Background

- Although uveal melanoma (UM) is the most common form of intraocular melanoma, and the second most frequent melanoma after cutaneous melanoma (CM), UM 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 [1, 2].
- The annual rate of new UM admissions in England is estimated at 1 per 100,000 persons and has remained stable, relative to population growth, over recent decades [2].
- ~90% of UM tumours involve the choroid, with the remainder confined to the iris and ciliary body.
- Despite radical intra-ocular intervention(s), half of patients with a stage I-III disease go on to develop metastatic disease (stage IV), predominately in the liver [3].
- Once metastatic disease occurs, mUM patients have few effective treatment options available [1].
- As such, reported median time-to-progression is 2-3 months and overall survival is 7-12 months [4].
- The Hospital Episodes Statistics (HES) dataset is a data warehouse containing details of all admissions, outpatient appointments and Accident and Emergency (A&E) attendances at National Health Service England (NHSE) hospitals [5].
- Collected monthly, HES aims to record every episode of care within NHS England and processes over 125 million admitted in patient, outpatient and A&E records each year.

Objectives

- Given the rare and aggressive nature of (m)UM, there are limited data characterising the disease and treatment pathway of patients to inform an understanding of standard of care (SoC).
- To inform a real-world understanding of (m)UM SoC treatment pathways, this study aimed to:
  1) Identify a cohort of (m)UM patients within the NHSE monopsony, using the HES database [5].
  2) Compare characteristics and observations of the HES cohort against the published literature and modelled epidemiological estimates.

Methods

- Within the HES dataset (observational period: April 2012–March 2017), we identified a cohort of UM patients with malignant neoplasms of the choroid, ciliary body and iris (ICD-10: C69.3, C69.4), and no other prior cancer code [5].
- Of these identified UM patients, we then selected a cohort that subsequently experienced a non-eye-related cancer code during the observational period, that was clinically characteristic of a UM metastasis ([6], Table 3). This was considered to give a conservative estimate of the occurrence of metastasis in the overall UM cohort.
- Patients with an unspecified (C69.9) or benign (D31) neoplasm of the eye at their first inpatient admission followed by a C693 or C694 in later admissions, were also included if they had a subsequent liver metastasis (C787).
- To identify the expected incidence of mUM in the cohort, we developed an epidemiological model.
  - UK-specific incidence data for eye cancer (ICD-10 code: C69) were identified within national statistics reports [8] and a ratio of choroid, ciliary body and iris involvement (C69.3 and C69.4 with melanoma ICD-O-3 histology code range 8720-8790) were applied from a comprehensive US cancer registry [9], to derive age-specific and gender-specific incidence of primary UM in the UK.
  - These UM incidence cases were then segmented by disease stage (I, II, III, and IV) at initial diagnosis [10,11].
  - Using registry data for UM patients observed for 0-10 years [12] and ≥10 years [6] prior to their metastatic (mUM) diagnosis, an annual incidence of metastatic progression ("recurrence") from an originating stage I-III diagnosis were then derived. These were further adjusted for age and gender distribution to enable an adjusted annual estimate of “recurrence”.
  - The expected total number of mUM (“recurrence” + stage IV) patients within the NHSE population of (54.786 M persons in 2015) was then estimated.
- Patient characteristics were extracted from HES and descriptively analysed. These data were then compared to published literature [1-7] and the expected incidence population (epidemiological model) to validate the cohort as being a (m)UM cohort for future evaluation.

Results and Validation of the Cohort

- Over the observational period, we identified a cohort of 2,484 UM patients within HES (**Table 1**).
- 501 patients in this cohort were diagnosed with mUM (**Table 2**).
- The clinical characteristics of both the UM and mUM patients in these HES cohorts were considered similar to those reported in the literature (**Table 1 and Table 2**).
- The median time from UM to first mUM diagnosis was 283 days (range 0 – 1675).

Table 1. Characteristics of UM patients in the cohort compared to patients in the published literature

UM Cohort	HES (N = 2,484)		Literature
Age at UM diagnosis (years)			
Median	64		62 [7] *
Range	2-98		6 - 100 [7] *
Sex (N, %)			
Female	1,184	47.7%	48.2% [7] *
Male	1,300	52.3%	51.8% [7] *
Site of primary UM (N, %)			
Choroid	2,110	85.0%	73.6% [7] *
Ciliary body	253	10.2%	16.8% [7] *
Choroid + Ciliary body	19	0.8%	-
Undefined	101	4.0%	9.6% [7] *
Patients receiving enucleation (N, %)			
Left	357	14.4%	~30% [7] *, **
Right	351	14.1%	
None	1,777	71.5%	

* Excludes diagnoses of conjunctiva, cornea, retina, lacrimal gland, orbit & overlapping legions; ** from patients diagnosed 2000-2008

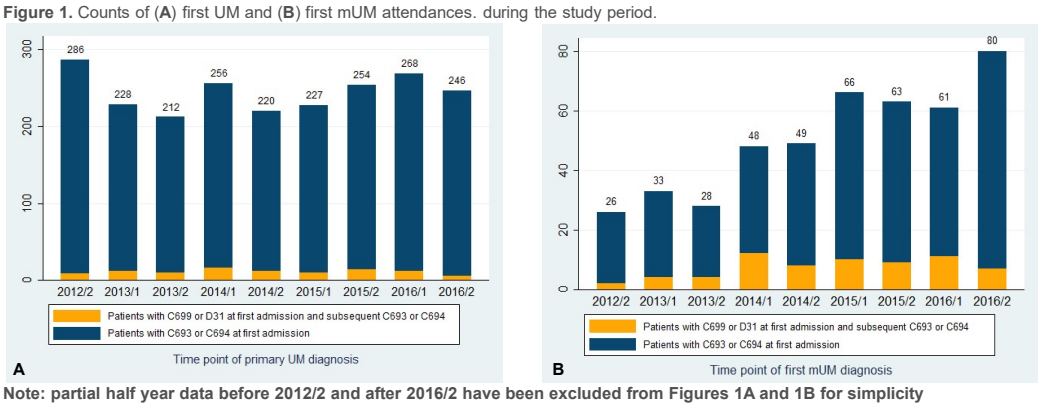
Table 2. Characteristics of mUM patients in the cohort compared to patients in the published literature

mUM Cohort	HES (N = 501)		Literature
Age at mUM diagnosis (years)			
Median	66		61 [6] *
Range	2-91		18-87 [6] *
Sex (N, %)			
Female	249	49.7%	47.5% [6] *
Male	252	50.3%	52.5% [6] *
Site of primary UM (N, %)			
Choroid	380	75.8%	na
Ciliary body	48	9.6%	na
Choroid + Ciliary body	5	1.0%	na
Undefined	68	13.6%	na
Patients receiving enucleation (N, %)			
Left	108	21.6%	49.2% [6] *
Right	98	19.6%	50.8% [6] *
None / unknown	295	58.2%	

* Patients that developed metastasis within 5 years of initial UM diagnosis

- The incidence of UM was stable over time; with 224 new patients on average being diagnosed every 6 months (range 212 – 286) (**Figure 1A**).
- In applying the reported annual incidence of new UM cases (6 to 10 per million UK persons [1,2]) to the population of NHSE, 329 to 548 new UM patients would be expected in 2015, respectively.
- In our HES cohort, 481 new UM patients were identified in 2015 (**Figure 1a**) - equivalent to an incidence of 8.8 per million of the NHSE population
- In applying our epidemiology model to the NHSE population, 118 new mUM patients would be expected in 2015.
- In our HES cohort, we identified 129 mUM patients in 2015 (**Figure 1b**).
- Consistent with the literature, the liver had the most metastatic involvement (67%), and was the most common site of first metastasis for mUM patients (**Table 3**).
- In later years (2014-2015), more patients in the HES dataset had admissions for liver metastasis in their first year following a UM diagnosis, compared to earlier years (2012-2013) (**Figure 2**).

Figure 1. Counts of (**A**) first UM and (**B**) first mUM attendances. during the study period.



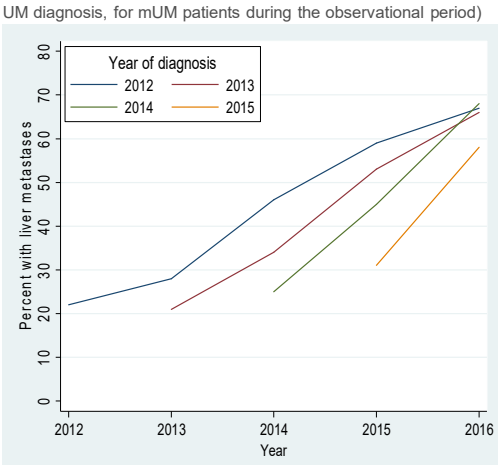
Note: partial half year data before 2012/2 and after 2016/2 have been excluded from Figures 1A and 1B for simplicity

Table 3. Sites of metastatic UM disease

mUM Cohort	HES (N=501)		Literature [6]*
Liver as 1st metastasis (N, %)			
	308	61.5%	82%
Site of metastasis at anytime (N, %) **			
Liver	334	66.7%	89.2%
Skin/soft tissue	164	32.7%	11.8%
Lung	124	24.8%	19.7%
Bone	83	16.6%	11.8%
Lymph nodes	34	6.8%	6.2%
Brain	30	6.0%	1.6%
Breast	19	3.8%	2.0%
Kidney	16	3.2%	1.0%
Adrenal	12	2.4%	2.3%

Note: * Within 5 years of first UM diagnosis; ** There can be multiple sites of metastases so totals may be >100%

Figure 2. Diagnoses of liver metastasis in each year, by year of UM diagnosis, for mUM patients during the observational period)



Discussion

- Recognising the limitations and the ‘*intent of data capture*’ when using any observational database; alongside the spontaneous nature of metastases; for a small rare disease population; and the recent improvements in surveillance for metastatic disease[1], the number of identified (m)UM patients in the HES cohort would be broadly consistent with expected estimates for the population.
- The disease characteristics of the UM and mUM patients identified in the HES cohort are also broadly comparable to the published data.
  - In our HES data, new mUM attendances increased over time (**Figure 1B**); this is likely a function of the length of time a patient in the cohort is observed.
  - There was slightly less overall liver involvement in our cohort (**Table 3**), which could be due to a limited follow-up period (<4 years for most patients), compared to the >5-year data reported [6].
  - There were also more skin/soft tissue metastases compared to other cohorts, which may be due to local variances in coding definitions for soft tissue involvement.
- National UM guidelines [1] introduced in 2015 and improved surveillance methods may explain the observed increase in the initial detection and rate of identifying liver metastasis during a patient’s 1st year of having UM diagnosis, in the later years of the HES cohort (**Figure 2**).

Conclusions

- The epidemiological and clinical characteristics of our (m)UM cohorts identified within HES appear consistent with modelled estimates and are validated by the published literature.
- This methodology enables a deeper insight into SoC treatment pathways and understanding of real world outcomes associated with an (ultra) rare disease [13], such as UM.
- Alongside the future introduction of an effective treatment, this methodology potentially provides the ability to assist with identifying, measuring, and coordinating the care pathway to ultimately improve outcomes for mUM patients.

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