The Fight Tumour Blindness (FTB!) Registry: Efficient capture of high-quality real-world data in uveal melanoma.

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Objective

To describe the development of a web-based data collection tool to track the management and outcomes of uveal melanoma patients.

Design

Description of a clinical registry.

Participants

Patients with uveal melanoma.

Methods

A panel of expert ocular oncologists, with input from other relevant specialties and individuals with expertise in registry development, collaborated to formulate a minimum dataset to be collected to track patient centred, real-world outcomes in uveal melanoma. This dataset was used to create the Fight Tumour Blindness! (FTB!) registry within Save Sight Registries.

Results

The dataset to be collected includes patient demographics and medical history, baseline visit, follow-up visit including tumour treatment, metastatic staging and surveillance, pathology and patient-reported questionnaires. The inbuilt mechanisms to ensure efficient and complete data collection are described.

Conclusions

The FTB! registry can be used to monitor outcomes for patients with uveal melanoma. It allows benchmarking of outcomes and comparisons between different clinics and countries.

Introduction

The first step in systematic collection of data to improve the outcomes of uveal melanoma (UM), the most common primary ocular malignancy in adults, is to agree on the minimum dataset that will be tracked[1]. Most centres that treat UM collect their patients' clinical information and outcomes or contribute to a national cancer registry. Some centres and countries collect a rich dataset, which has formed the basis of the cohort studies that have driven advances in management of patients with UM over the past 20 years. Efforts have been made to compare the data collected at different centres, including surveys and comparative cohort studies[2–4]. The Fight Tumour Blindness! (FTB!) registry is designed for uniform and efficient capture of real-world clinical data in UM to facilitate this[5].

FTB! is a module within the Save Sight Registries (SSR). SSR was established fifteen years ago, initially focused on macular conditions, and now with modules in most fields of ophthalmology. It has generated a wealth of real-world data on outcomes of treatments in clinical practice[6–8]. Its data has led to important observations, such as the link between better long-term visual outcomes in neovascular age-related macular degeneration in countries that inject intravitreal anti-vascular endothelial growth factor inhibitors more frequently[9]. Such findings highlight the potential for FTB! to enable benchmarking of outcomes in UM, which may inform future management decisions and resource allocation.

FTB! will compare real-world practice patterns and clinical outcomes between centres and countries using a web-based platform. It will prospectively collect data on primary tumour treatment, local control rates, incidence of side effects, pathological features, metastatic rates and patient-reported outcomes. The interface will be designed to facilitate clinical decision support by using graphical representations of the patient journey. In this paper, we describe the principles of design and development of the FTB! registry.

Methods

Structure of the FTB! Registry

The FTB! project has separate steering and publishing committees. The global steering committee consists of a representative group of ocular oncology specialists from Australia and a founding member of SSR from Switzerland (members – Roderick O'Day, John McKenzie, Li-Anne Lim, Max Conway, Lindsay McGrath, David Sia and Daniel Barthelmes). This committee oversees the general development of the project, refinement of data fields and registry usage. As new countries join FTB!, they will be able to form their own national steering committees to manage their involvement, as has occurred in other SSR modules.[10] The publishing committee oversees the research output of FTB! by generating and reviewing submissions for potential publications, and ensuring adherence with publishing guidelines.

Defining the Minimum Dataset and System Design

The global steering committee of ocular oncologists defined the minimum dataset by consensus, focusing on parsimony, validity and adherence with current American Joint Cancer Council Staging (AJCC).[11] Input from expert ocular pathologists, medical and radiation oncologists and radiation physicists was sought for relevant data fields. A literature review identified potential variables to be collected, which were presented to the global steering committee. Consensus on the final dataset was achieved after multiple structured videoconference meetings. The completed module was endorsed by the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Ocular Oncology Specialist Interest Group as the primary modality for data collection of ophthalmic outcomes for UM patients in our centres. This dataset will be used across all centres and countries participating in FTB!

Strategies to ensure high fidelity data collection include using the minimum number of data fields as possible, avoiding 'free text' data fields in favour of pre-specified options from a drop-down menu and limiting values to pre-determined ranges. AJCC Stage for UM involving the choroid or ciliary body is automatically calculated by FTB! to avoid imputation errors. Tooltips were included to provide clinicians additional information so that questions are answered uniformly. Data can be 'saved' if

incomplete and then ‘finalised’ when complete. The most important data fields are labelled ‘mandatory’, such that episodes cannot be ‘finalised’ until all have been completed. Only finalised data are available for analysis and reporting.

Software and Data Security

The FTB! software is a web-based application, which was developed using freely available software such as Apache, MySQL, PHP and RubyonRails, allowing it to be run on different operating systems. Data is typically entered into FTB! through a web interface.

All transmissions of data are encrypted using 128-bit encryption (Secure Sockets Layer). The data are stored and backed up on secure servers at the University of Sydney’s Information and Communication Technology Department. Anonymity of clinicians is closely guarded, providing confidence to enter data completely, including complications. Each clinician can only see their own data with summary data from the entire registry cohort allowing benchmarking against their peers in the registry. Clinicians can withdraw their data from the registry at any time without providing a reason. Clinicians are contacted about planned publications and can opt out of having their data included in the analyses. Clinicians can download their own data at any time as a text file in comma-separated variable format, to undertake their own analyses. The software also has a built-in statistical report providing an overview of patients, primary tumour treatment, local recurrence and visual outcomes.

Funding

FTB! has been supported by a research grant from the Ophthalmic Research Institute of Australia. SSR is supported by the RANZCO, and industry. The guidelines for the relationship between SSR and industry have developed over the last decade, and FTB! apply these. Industry will never have access to raw data, or involvement in data entry. Industry may commission a publication, with oversight from the publication committee, but will not play a role in the design, data extraction, analysis or writing of the manuscript. Industry may be provided a copy of an advanced draft of the manuscript and the option to provide non-binding comments. Participation in the project is free to clinicians.

Ethical considerations

Users must satisfy local regulations and the requirements of their institutional Human Research Ethics Committee (HREC). FTB!, in contrast to other modules in SSR, is able to collect non-mandatory identifiable data including name, postcode, date of birth and sex. This is to enable data linkage with national death indices. The only mandatory identifiable data required to be entered is hospital number, date of birth and sex. All patients are required to provide prospective written, informed consent. The project was approved by the Western Sydney Local Health District Human Research Ethics Committee. (2020/ETH00956) Overarching ethical approval was also obtained from the RANZCO HREC to streamline the process for participating private practices in Australia and to ensure, from a central governance perspective, that all users were aware and informed of their ethical responsibilities.

Results

Dataset

The FTB! registry has six domains: patient demographics and medical history, baseline visit, follow-up visit including tumour treatment, metastatic staging and surveillance, pathology and patient-reported outcomes (PROMs). The mandatory data fields to be collected by FTB! are outlined in Tables 1-6. These are contained as separate forms within the online module and are presented initially as core parameters, which expand depending on clinician response facilitating efficient data entry. There are only five free-text fields, as these tend to collect data that is not interpretable.

In addition to the baseline demographics outlined in table 1, patient name, ethnicity, date of birth, postcode, smoking status, ECOG status, germline status, Fitzpatrick skin type, iris colour and original hair colour can be entered. Table 2 details the data to be collected at a baseline visit. The clinical features that determine AJCC stage, as well as the recognised multimodal imaging risk factors for malignant transformation of choroidal naevi are collected. Distinction is made between new onset melanomas and growth of a previously diagnosed choroidal naevus, which may allow analysis for differences in outcomes between these patient cohorts. Tables 3 and 4 outline the data to be collected at follow up and treatment visits. Treatment visits are intended to capture tumour specific treatment, for localised and metastatic disease, as well as neoadjuvant, primary tumour and adjuvant treatments. The most commonly performed treatments and complications are listed first.

Table 5 contains the metastatic disease assessments, including staging, surveillance, and risk assessment. In the patient home screen these are readily visible to the clinician, and can act as a visual reminder to ensure they are being conducted according to local protocols. Table 6 details the pathology tests performed in real-world clinical care of patients, as well as some research and emerging investigations, such as next generation sequencing and liquid biopsy. The histology parameters collected are based on the minimum dataset outlined by the Royal College of Pathologists[12].

FTB! includes the Impact of Vision Impairment (IVI) questionnaire, a validated PROM, in line with other SSR Modules. UM specific PROMs can be added in the future.

Discussion

To facilitate the comparison of outcomes in patients with UM managed at different sites, we have created an efficient, web-based platform to collect high quality data. The system has been designed to extract the maximum amount of information from a minimal dataset[13]. Clinical care and research in UM are in a period of rapid change, from early diagnosis using multimodal imaging to novel treatments for metastatic disease. Uniform collection of data at all participating centres may aid translating these advances into better UM care for all stakeholders by facilitating direct comparison of outcomes. The minimum dataset was defined by an expert panel using an iterative process and the finished module endorsed by the RANZCO Ocular Oncology Specialty Interest Group. Identifiable data can be collected to allow data linkage with death indices for most accurate mortality tracking, but is not mandatory for centres and countries that do not wish, or have the capacity, to do so.

Observational registry-based studies offer advantages for stakeholders at every level. FTB! can be used by physicians to benchmark their results by anonymously comparing their outcomes with their peers. Clinic flow can be improved with graphical representation of the patient journey. PROMs can be evaluated and correlated to clinical outcomes. Physician bodies can ensure that management and outcomes meet accepted guidelines. Government and industry stakeholders can see how interventions are being used and their effectiveness in a general patient population. Data can also be used to develop new hypotheses regarding the management of specific patient populations. Ultimately, the implementation of an international outcomes registry in UM may improve outcomes for all stakeholders.

UM is an ideal condition for observational registry-based studies for a number of reasons. Rare diseases are well suited to registry-based collaboration, as demonstrated by the recent Global Retinoblastoma Study, which generated important findings from small numbers of patients at individual sites collecting the same data fields[14]. Randomized controlled trials in UM face significant cost and ethical barriers, and none have occurred since the Collaborative Ocular Melanoma Study, which finished recruiting twenty-five years ago[15]. Significant variation in primary tumour treatment exists, including whether to treat small tumours, radioisotope & radiation dosing used in plaque brachytherapy and type of external

beam radiotherapy offered[16–19]. Unsurprisingly, profound differences in clinical outcomes occur, best exemplified by the fact that local tumour control rates with plaque brachytherapy ranges from 59 to 100%[20]. In addition to the many existing questions regarding the traditional management of UM, FTB! may aid the implementation of new developments in UM, including neoadjuvant systemic therapy and the treatment of metastatic disease[21–25].

We have taken steps to achieve high quality data entry into FTB!, by addressing the limitations that often affect observational studies [13,26]. The SSR modules have evolved with time to incorporate multiple quality assurance measures. Training is provided to all clinicians prior to using the registry. Visits can only be finalised if all mandatory data fields are completed within predetermined ranges. Free-text data fields are avoided throughout. Loss to follow-up can be reduced by the ability to transfer a patient's data from one clinical to another as long as they are both participating in the project. Data quality review is planned to be conducted at regular intervals. This will likely include independent assessors of the verify that the source data matches the data in the FTB! registry at consenting clinician's practices, as has been performed in other SSR modules.[27]

Conclusions

We have described the development principles and data fields to be captured of a registry for the outcomes of patients with UM. This will allow the analysis of a number of important, potentially modifiable variables, such as the effect of different treatment patterns on local tumour control. New treatments will be evaluated as they are introduced into practice.

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Table 1: Basic Demographics to be collected

Core parameter	Answer Options	Conditional parameter	Answer Options
Medical history	Hypertension Diabetes mellitus Hypercholesterolaemia Other medical history		
Cancer history	Yes		
	No	Type of cancer	Cutaenous melanoma Mesothelioma Renal cell carcinoma Non-small cell lung cancer Non-melanoma skin cancer Other
HLA-A2 status?	Positive Negative Unknown Not done		

Table 2 – Baseline Visit Form

Core parameter	Answer Options	Conditional parameter	Answer Options
Ocular comorbidities	Amblyopia Cataract Diabetic retinopathy Glaucoma Macular degeneration Retinal vein occlusion Other		
How was the tumour diagnosed?	Asymptomatic (detected on routine examination)		
	Visual disturbance		
	Growth of choroidal naevus into melanoma	Date naevus first diagnosed	Date
		Type of growth	Thickness Horizontal diameter Both
	Unknown		
Tumour status	New onset melanoma		
	Previously diagnosed melanoma - initially monitored	Date melanoma first diagnosed	Date
	Recurrent choroidal melanoma	Prior oncology treatments	Transpupillary thermotherapy Photodynamic therapy Plaque brachytherapy Stereotactic photon radiotherapy Proton beam radiotherapy Surgical resection Observation Other
Symptoms attributable to tumour	Asymptomatic Decreased vision Photopsia Pain		
Site	Iris	Clock hours involved	≤ 3 > 3
		Secondary glaucoma	Yes / No
		Scleral extension	Yes / No
	Ciliary body	Ciliary body involvement	Pars plana Pars plicata Angle
	Choroid	Distance to optic nerve	Value (mm)
		Distance to fovea	Value (mm)
		Subretinal fluid	No Exudative retinal detachment Around tumour visible on fundus examination Only detected by OCT
		Lipofuscin	No Visible on fundus

			examination Only detected by autofluorescence
Location	Macula		
	Juxtapapillary	Number of clock hours touching the disc	Value (0-12)
	Superior		
	Inferior		
	Nasal		
	Temporal		
Extrascleral extension	≤5mm >5mm No		
Ultrasound features – reflectivity	Low Medium High		
Ultrasound features - shape	Dome Collar stud Bilobed Other		
AJCC Stage (cT) (calculated)*	cT1a – cT4d		
AJCC Stage (N, M)	NX / N0 / N1 MX / M0 / M1		
Tumour size max basal diameter	Value (mm)		
Tumour size max thickness	Value (mm)		
Visual Acuity	Value (ETDRS letters)		

* automatically calculated for choroidal and ciliary body melanomas. Iris melanomas require manual entering.

Table 3 – Treatment Visit Form

Core parameter	Answer Options	Conditional parameter	Answer Options
Indication	Primary ocular treatment Local recurrence Neoadjuvant (before local therapy) Adjuvant (after local therapy) Metastatic disease Other		
Treatment types	Plaque brachytherapy	Plaque type	Ruthenium Palladium Iodine Other
		Plaque size	
		Plaque shape	Notched Circle
		Dose delivered to scleral base	
		Dose delivered to tumour apex	
		Basal dose rate	
		Dose delivered to fovea	
		Dose delivered to optic nerve	
	Enucleation		
	Photodynamic therapy		
	Transpupillary thermotherapy		
	Endoresection		
	Exoresection		
	External beam radiotherapy	Radiotherapy type?	Protons Photons
		Total Dose	
		Fractions	
	No primary treatment given - monitoring		
	Drug therapy	Delivery method	Intravenous Oral Subcutaneous Other
		Drug used	Nivolumab Ipilimumab Crizotinib Darovasertib Dacarbazine Pembrolizumab IMCgp100 Sunitinib Tamoxifen Trametinib Thalidomide Valproic acid Other

	Liver-directed therapy	Therapy Type	Surgical resection Chemoembolization Bland embolization Immunoembolization Radiofrequency ablation SIRT Percutaneous hepatic infusion of melphalan (Delcath) Other

Table 4 – Follow-up Visit Form

Core parameter	Answer Options	Conditional parameter	Answer Options
Visual acuity	Value (ETDRS letters)	Cause of reduced vision	Pre-existing ocular comorbidity Local effects from tumour Side effect of tumour treatment Unknown
Tumour size max thickness	Value (mm)		
Local tumour control?	Yes		
	No	Location of tumour recurrence	Edge Central Extraocular
Metastatic disease?	Yes / No / Unknown		
Ocular complications?	Neovascular glaucoma Proliferative radiation retinopathy (NVI / VH / NVE / NVD) Radiation CMO Toxic tumour syndrome Radiation optic neuropathy BRVO / CRVO Macular atrophy Scleral necrosis Dye eye syndrome Cataract Scleral perforation Other event		
Ocular treatment?	Yes	Treatment	Aflibercept (Eylea) Bevacizumab (Avastin) Bevacizumab (Mvasi) Brolucizumab (Beovu) Faricimab (Vabysmo) Ranibizumab (Lucentis) Ziv-aflibercept (Zaltrap) Dexamethasone implant (Ozurdex) Triamcinolone Periocular steroid injection Oral steroids Retinal laser photocoagulation Transpupillary thermotherapy Photodynamic therapy Vitrectomy Glaucoma drops Glaucoma surgery Endoresection Cataract surgery

	No		

Table 5 – Metastatic Staging and Surveillance Form

Core parameter	**Answer Options**	**Conditional parameter**	**Answer Options**
Indication	Staging		
	Surveillance	Planned frequency (months)	
		Planned duration	Up to 2 years 3-5 years 6-10 years > 11 years indefinite
	Risk assessment	Tool used?	LUMPO Other (opens to free text field)
		10-year estimated mortality?	Value (%)
Investigation Type	LFT		
	CT MRI USS	Area imaged	Whole body Brain Chest Abdomen Pelvis Liver only Kidneys only Other
	PET-CT		
	Tissue biopsy	Site of biopsy	Liver Lung Lymph node Skin Brain Soft tissue Other (opens to free text field)
	Other		
Result of Investigation	Normal		
	Equivocal - metastatic disease suspected	Planned further management	Tissue biopsy Interval assessment
	Metastatic disease proven	Date metastatic disease diagnosed	
		Metastasis location	Liver Lung Lymph node Skin Brain Soft tissue Disseminated Other (opens to free text field)

Table 6 – Pathology Form

Core parameter	Answer Options	Conditional parameter	Answer Options
Specimen type	Enucleation		
	Ocular biopsy	Approach	Transcleral Transretinal Post-enucleation Endoresection Other
		Sampling method	FNABx Forceps Scalpel Vitrector Other
		Number of fragments	Nil visible <= 2 3-5 >5
		Colour	Dark Light Red
Test performed	Histology	Site of tumour	Iris Ciliary body Choroid
		Thickness of tumour	
		Largest basal diameter	
		Macroscopic extraocular extension	No <5mm >5mm
		Diffuse growth pattern	Yes / No
		Cell type	Spindle Epitheliod Mixed
		Mitotic count	
		Close PAS loops	Yes / No
		BAP1 immunohistochemistry	Wild type Mutant Not done
		PRAME immunohistochemistry	Wild type Mutant Not done
	Cytogenetics	Findings	Disomy 3 Monosomy 3 Partial deletion of chr 3 Normal 8q 8q gain 8q gains (multiple) 6p gain Other (opens to free text field)
	Molecular diagnostics / NGS	Type of test	Targeted panel Whole exome sequencing Whole genome sequencing Unknown

		Mutations found	GNAQ Q209 GNAQ R183twun GNAQ GNA11 Q209 GNA11 R183 GNA11 BAP1 SF3B1 R625 SF3B1 EIF1AX PLCB4 D630 PLCB4 CYSLTR2 L129 CYSLTR2 MBD4 Other (opens to free text field)
	GEP / Decision-DX	Findings	Class 1a Class 1b Class 2
	TCGA	Findings	1 2 3 4
	Liquid biopsy		
	Other		
Was the specimen biobanked?	Yes / No		
Conclusive test?	Yes / No		