The Functional Imaging of Tumours Study

Foreword

The Functional Imaging of Tumours Study has been aiding the translation of new imaging methods into clinical practice for nearly 20 years. In partnership with the Children's Cancer and Leukaemia Group and the University of Birmingham as study sponsor, we have formed a world leading consortium of imaging centres and experts in the field allowing the collection and analysis of medical imaging from children and young people from around the country. In this way, the study has provided a platform for developing, evaluating and integrating new imaging methods into clinical practice. Funded by many of the major grant awarding bodies and with links to clinical data and tumour biology, the study has generated numerous publications on diagnosis, prognosis and improved understanding of children's tumours as well as being associated with national and international prizes. The study has had a major input to national and international guidelines for the use of imaging and through this helped improve the care of many children with cancer. In these days of ever increasing reliance on computerised data analysis and the emergence of artificial intelligence, the study takes on increasing significance and it is time to capitalise on the infrastructure we have developed over the past 20 years to ensure that we can continue to improve the survival rates and lives of children and young people with cancer. Kindly hosted by Aston University we are meeting to plan an exciting future for this seminal study.

Andrew Peet – Chief Investigator

An historical perspective

In the 1990s considerable interest had developed around a set of imaging techniques which could probe tumour properties, called functional imaging. One of these, magnetic resonance spectroscopy could provide metabolite profiles of tumours and became a focus for two academic oncologists Andrew Peet and Richard Grundy who thought that magnetic resonance spectroscopy and tumour molecular genetics could improve not only our understanding of tumour metabolism but brain tumour characterisation in general. Following some earlier successes, there was also an intent to use computerised pattern recognition for the analysis, the beginnings of Artificial Intelligence. Initially funded by a local charity, the study was set up as a single centre study in Birmingham where they were both based. The hospital did not have an image storage PACS system then and a specific grant was awarded to set up a digitalised web accessible database which was set up by Kal Natarajan, a clinical scientist in computing. Substantial funding came from the Department of Health in 2002, and with the support of the Children's Cancer and Leukaemia Group (then the UKCCSG and acting as a Clinical Trials Unit), the project became multi-centre. A new web accessible database was developed with Theo Arvanitis, Engineering at University of Birmingham. We were well supported by key figures at the major centres in the UK and the first patient was recruited by oncologist Darren Hargrave, then at RMH, who has continued to be a strong supporter. We soon became partners in the EU Framework 6 Project eTumour which had similar objectives across the whole age range and provided an early example of data sharing between projects. Input from physicists has always been essential to this venture and the funding allowed recruitment of Nigel Davies and the first PhD student, Martin Wilson. Increasing success led to the award of a Cancer Imaging Programme Grant by Cancer Research UK, EPSRC, MRC and NIHR. Study co-ordination became increasingly important and Jane Crouch undertook this from Birmingham, which had become the sponsor. Over the years, the study has broadened in scope for imaging types and tumour locations but is still faithful to the initial concept of probing childhood tumour properties with imaging and linking these with tumour biology. The projects supported by the study have been funded by most of the major funding bodies and many smaller charities. A large number of papers have been published ranging from technical advances to clinical studies of added value. The findings have been presented throughout the world and are increasingly being incorporated into a clinical decision support tool.

Overview of the Functional Imaging of Tumours Project

The Functional Imaging of Tumours Study is a single arm observational study (REC 04/MRE04/4; IRAS 32486) currently sponsored by the University of Birmingham. There are approximately 1700 patients recruited to the study from 11 centres in the UK. The study originally opened in Oct 2004 as the MRS of Brain Tumours study and the scope was widened in terms of imaging and tumour type in February 2012 when it was given its current name. Patients are registered on the study via a web accessible database housed at the University of Birmingham (https://rde.cclgfig.bham.ac.uk). Demographic, clinical and imaging data can then be uploaded to the database on the recruited patients. Since the start of the project, Andrew Peet, University of Birmingham, has been the Chief Investigator with Richard Grundy (University of Nottingham) being the deputy. The study co-ordinator is currently Sara Burling, Birmingham Children's Hospital. Theo Arvanitis, University of Birmingham, has led the team which has developed the database in collaboration with the investigators.

The aims of the project

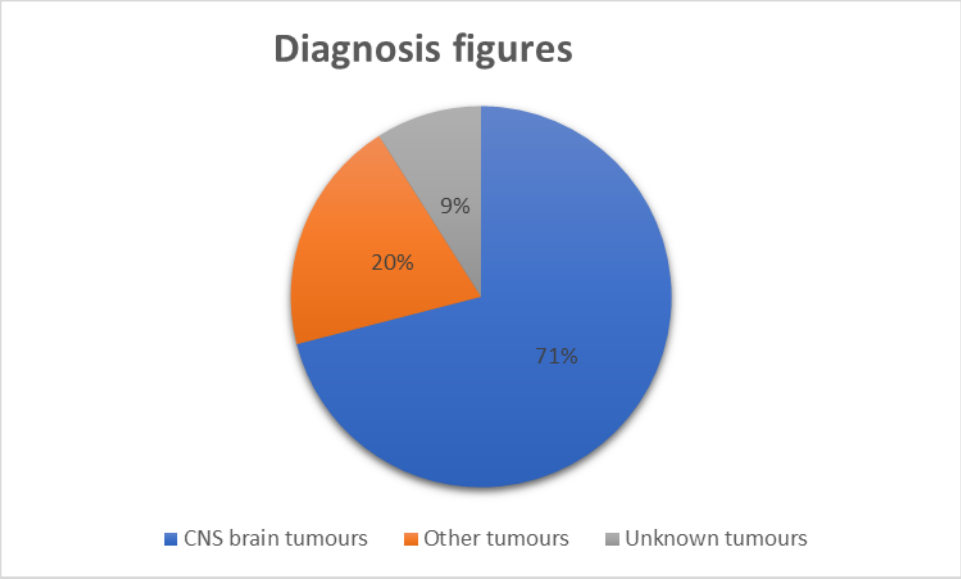
To develop functional imaging methods for the diagnosis, management and understanding of tumours in the fetus, children and young people (up to 25 years of age).

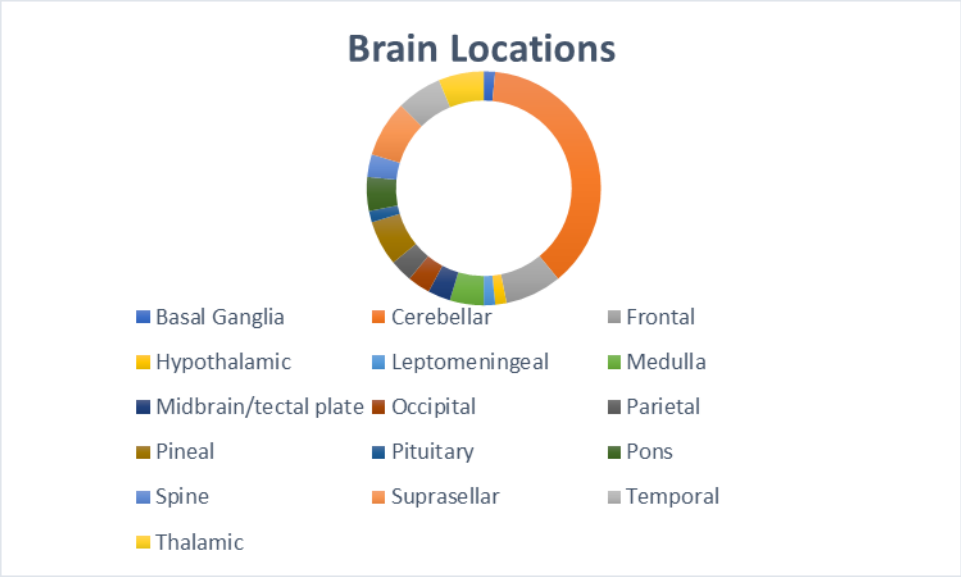
To correlate functional imaging with in vitro studies of the biology of tumours, in particular in vitro Magnetic Resonance Spectroscopy (MRS) and tumour genetics.

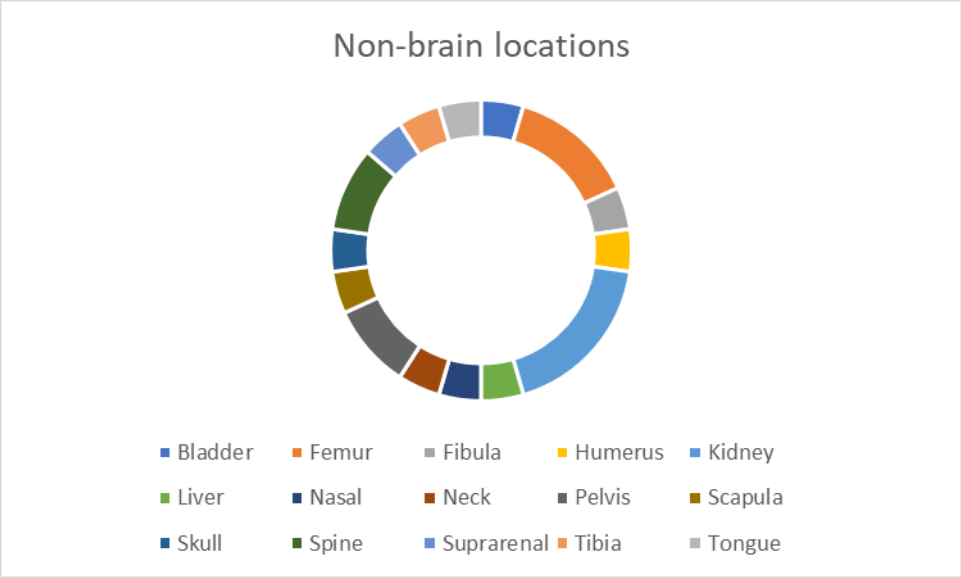
From a practical point of view, functional imaging has been taken to be advanced MRI techniques, dominated by diffusion imaging, perfusion imaging and spectroscopy. Consent can be taken within the study for an additional 10 to 15 minutes of scanning time to be added to a routine clinical scan. This has allowed us to acquire data on new techniques with the aim of gaining evidence towards them becoming part of routine clinical practice. This strategy has become so successful over the years that in many cases all imaging is performed as part of routine clinical care. Consent is then often taken after the scan has been performed purely to allow transfer, storage and use of data.

Data Acquired

The database has forms for patient data and clinical data in addition to imaging data. There are forms for symptoms at diagnosis, surgery, histology and links to any clinical trials the patient is enrolled on. In addition, there is a form for the diagnostic MRI which includes information on tumour size, location and metastatic status. All of these forms except symptoms are replicated at relapse. There is a form to record date of death and whether this is related to the tumour as well as the time the status was last recorded if the patient is alive. Of course, as with all databases forms are not always completed. In particular, relapse information is often quite sparse. The following charts give an overview of the cases enrolled on the study.







Funding

The Functional Imaging of Tumours Study has been funded by a large number of grant giving bodies over the years. Early funding was obtained from the Department of Health and Birmingham Children's Hospital Charities closely followed by an EU Framework 6 project eTumour. The consortium was later awarded a Cancer Research UK / EPSRC Cancer Imaging Programme. More recently, the study played an important role in the multi-funder initiative Health Data Research UK. In general, grants have been awarded for projects with strong scientific and clinical aims where a portion of the grant has been allocated to running the study itself. The study is listed on the NIHR Portfolio and accrual is uploaded to the portal to allow funds to be obtained by recruiting centres through their CLRN. This has allowed the study to use the infrastructure set up in the recruiting centres for running clinical trials. In general, extra funding has not been available for data acquisition and upload via research grants which have focussed on funds required for analysis with some funds for study co-ordination, clinical physics and database development. A key grant currently linked to the project and recognised by the sponsor is the Experimental Cancer Medicine Paediatric Network which largely funds research nurses but has a funded data theme.

Data Access

It is stated in the patient information sheets that "Researchers authorised by this "CCLG Functional Imaging Group" will analyse the data". From a practical point of view, the "CCLG Functional Imaging Group" has developed into a consortium which has applied for grants, many of which have been successful. The successful grant applications have then defined the projects and their governance has been via the management committees of the specific funded project or programme. Data access for these funded projects has then been through bespoke formal contracts (research collaboration agreements) with the University of Birmingham. More recently, requests have also come to the Chief Investigator for data access for specific projects and then advice from other members of the Group has been sought where appropriate. At present, we allow access to the data for those with an appropriate defined project and a personal contract with the University of Birmingham. These contracts can be obtained relatively straightforwardly. Over the past couple of years, we have been in discussion with the sponsor regarding a more general data access agreement. This requires contracts to be made with the data collection centres which is currently in process and a contract for outgoing data which has been drafted.

There are several other databases in the UK which could provide useful extra data on patients recruited to the Functional Imaging of Tumours Study for example biological data and clinical trials data. We have managed to capitalise on this for linkage to the Low Grade Glioma 2 Trial and Medulloblastoma molecular biology via the CCLG Tissue Bank and Newcastle repositories to achieve the wider aims of the study. We have also explored the possibility of wider data linkage and integration. However, assessment of the Functional Imaging of Tumours Study by the CRUK Data Innovation Award Team deemed the study unsuitable for wider data sharing beyond the objectives of the original study.

Publications and other outputs:

The study has been highly successful in publishing papers using both the data on the database and the expertise of the consortium, with around 150 papers, reviews, book chapters and guidelines. The study has been directly involved in 83 papers of original research of which 7 have been specifically focussed on the laboratory based biological studies aspects. Collaborative studies and studies using the expertise developed within the consortium account for 44 papers. Many of the publications have relied on multi-centre data which has been a particular strength. This was well illustrated by an analysis of perfusion in brain tumours by Stephanie Withey which won the Thomas L. Slovis Award for the Best Basic Science Paper appearing in Pediatric Radiology in 2022. In addition to paper publications, the findings have been presented at conferences nationally and internationally with a large number of abstracts being accepted. There has also been an important training element to the Functional Imaging of Tumours Study with around 20 graduate students being awarded PhDs and numerous post-doctoral research fellows furthering their training. A whole cadre of scientists and clinicians have been trained, almost spanning a generation.

Appendix

Thoughts about Imaging Data Transfer, Anonymisation and Pseudoanonymisation of Imaging Data based on experience of FI of Tumours Project –

Perhaps the single most challenging aspect of the project has been preparation and transfer of the imaging data from the hospitals to the database. This is far from being a solved problem and improvements are still required. For this reason, it is probably worth recording our experiences and thoughts on the matter.

Anonymisation of imaging data is a challenge and there are no perfect tools available. Most, pragmatically, just deal with DICOM data so that there is at least some level of agreed standard. The Functional Imaging of Tumours study has taken that viewpoint. Even with this restriction, there are various challenges that remain.

From a broad perspective, personalised data can be in the header or directly "burnt" into the image.

There is no reliable way of detecting information "burnt" into the image and so the images should be visualised and redacted by hand. This is a tedious and time consuming process. Some AI algorithms are being developed to detect "burnt in" information but these are not yet good enough to be used on their own without visualisation. This is one of the aspects that data management staff find unsatisfactory and is a constant complaint from those involved.

For the header information, there are standard tags that are well defined and can be identified and anonymised - eg name. There are many tools which will do this. However, there are also "private" tags which are not defined within the DICOM standard. They tend to be used by scanner manufacturers for specific pieces of information of importance to them. Since these private tags are not defined, they can potentially contain patient identifiable information. For this reason, many anonymisation tools just completely delete them. This is a safe approach but risks removing important information which may be required for quantifying the images.

The reality is that imaging data formats change constantly and any anonymisation tools need continual "maintenance" to keep them working. This is a problem for clinical trials that may continue for many years since this needs to be factored in. If a tool from an academic group is chosen then it would need long term funding and a reasonable chance of continuing to be active over a long time period. If a commercial solution is chosen then you need to be reasonably certain that the product and company will be available for the duration of data acquisition. That really rules out all "SME". One option is to shift the problem to the data acquisition team, so anonymise the data before it leaves the scanner. This is usually pretty robust and likely to be available for the lifetime of the scanner. I think these tools tend to remove all the private tags but if you just want to visualise and not quantify the images that is fine (basic tumour sizes usually still work). Of course, it does mean that there is not uniformity of image anonymisation since all scanner manufacturers will have their own tools.

For the functional imaging study, we decided to develop our own image anonymisation tool which anonymises the fields we know contain personal data and keep tags that we need information for image analysis purposes. However, the tool needs regular maintenance as data formats change. It has recently been re-developed by Theo Arvantitis' team and so is pretty robust and much quicker than it was. Long term underpinning funding for this task is an important aspect of any ongoing imaging study. This requires input from both a software engineer and an MR physicist.