Minutes

SANON-SINAPSE Neuro-oncology Research Meeting
Dundee, 8th October 2015

Summary and Action Points:

- **PET imaging for brain tumours:** A t-con is to be set-up up to discuss a potential FET PET imaging grant application to set-up the production of 18FET in one of the PET cyclotron units. Subsequent email discussion has identified 18F-FACBC as a potential candidate tracer.

  Sally/Anthony/Irene

- **fMRI in neuro-oncology:** Cyril and colleagues from other centres to set-up a feasibility study looking at harmonisation of fMRI protocols

  Cyril/Arnab/Avinash

- **Small animal MRI to measure invasion in glioblastoma xenografts:** Antoine to liaise with Cyril regarding integration of multiparametric data sets.

  Antoine

- **Next meeting:** General agreement that annual meetings are warranted and valuable. Organise TC before end of 2015 to discuss date, venue, content and sponsorship for 2016 meeting.

  Irene/Anthony

Update on SINAPSE
Dave Wyper
Encouraged audience to join SINAPSE www.sinapse.ac.uk. Website updated weekly.

Update on SANON
Avinash Kanodia
Established 2006.. One of main roles is to publish guidelines for Scotland on treatment of brain tumours.
Looking to the future:

- National MDT for rare tumours. No consensus on this yet.
- Further national guidelines
- Further consolidation of existing guidelines to provide best care

A Scottish, British and International review of the application of PET for brain tumours
Sally Pimlott (Glasgow)
FDG PET is the most widely available, but not suitable for brain tumour imaging. Other targets that can be used for brain tumour imaging:

- FLT (marker of thymidine kinase)
- CHT (choline)
- Hypoxic markers
- Amino acid tracers (LAT transport system)
- Somatostatin receptor imaging (especially in conjunction with Yttrium-90
- TSP0 (neuroinflammation). They use this in Manchester
- Angiogenesis markers e.g. integrins

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FDG PET imaging: Generally not thought to be useful for imaging of brain tumours because of the high normal uptake in normal brain. There is a CRUK study looking at FDG PET currently.

Amino-acid imaging: Taken up by LAT1 transporters. No uptake in healthy brain cells and the tracer is transported across blood brain barrier (BBB) without need for BBB breakdown.
E.g.
11C-methionine: Short half life (20 minutes) – main disadvantage as means that it cannot be made in one central lab and transported across Scotland/UK. Considered gold standard for brain tumour PET imaging. It has been used since the 1980s. Can give an indication of how aggressive a tumour is.
18FET (fluroroethyltyrosine): It has been used since 1990s. Longer half life than methionine. It is an artificial amino-acid tracer and can obtain images comparable to using 11C-methionine.
18F-DOPA: Analogue of phenylalanine but there is uptake in normal striatum.
18F-FACBC: little clinical data in GBM but novel and being developed in Glasgow for prostate cancer study

Overall amino acid PET imaging may help when MRI inconclusive, recurrence post RT, guiding biopsy, treatment planning, distinguishing true from pseudoprogression.

Dynamic PET imaging (over a longer time period rather than one point in time): Also get glioma grading and can help in distinguishing RT changes from true progression.

Choline based PET imaging: Uptake affected by BBB.

FLT PET imaging: Thymidine kinase 1 overexpressed in proliferating tumour cells. This imaging can be interfered with by drugs that inhibit S phase of the cell cycle (anti-metabolites).

Hypoxia-markers PET imaging: Correlation with HIF-1alpha inconsistent.

What is current practice in Scotland?
Aberdeen: No routine PET for brain tumours. Do have access to 11C-methionine.
Glasgow: No routine PET for brain tumours. 201Tl SPECT imaging, 123I-IMT SPECT (amino-acid).
Edinburgh: No routine PET for brain tumours.
Dundee: No routine PET for brain tumours.

There are limited commercial suppliers of tracers in the UK.
Brief discussion about international research that is currently ongoing.

Discussion/Questions

Main points:

- Cost/benefit of using PET: funding is a major issue. F-DOPA – if already being made Scotland then this would be a good tracer to use in other centres in terms of cost reduction. It is only made in Edinburgh currently and low on their priority list. Striatum uptake is an issue in terms of diagnosing tumours in that area however it could also be a benefit as that area could be used as a control uptake check or could do a baseline scan to see uptake at baseline. The "top priority" in Edinburgh currently are the cardiac tracers.

- There are challenges in getting approval for new tracers to be used.

- Will PET-CT scans done pre-operatively offer any advantages if the patient is going to have an operation anyway and tissue will be obtained at that time for diagnosis?
- PET-CT is likely to be most useful in the post-operative setting to distinguish true versus pseudoprogression.
- Any validated studies with amino acid tracers for diagnosing pseudoprogression? Memorial experience. FET/Methionine are the tracers being investigated in Germany/Switzerland for this purpose.
- There is a need for more clinical input into decision about which PET tracer to prioritise e.g. F-FLT versus F-misonidazole as this is a limited resource.
- In 2016 the UK are implementing European guidelines that will mean it is hopefully easier/less regulatory barriers to making and using these tracers.
- PET versus MR-spectroscopy: MR-spectroscopy not as reliable.
- Spectroscopy: can get multi-voxel and single-voxel images but it still has limitations e.g. haemorrhage will distort the images. It is currently used as a problem solving tool rather than a definitive diagnostic tool.
- Could PET-CT be combined with trials looking at radiosensitisers and radiotherapy for GBM e.g. PARADIGM trial?
- Aberdeen has had PET for longer than Glasgow and Edinburgh. Timelines are currently long for producing the markers.
- You want to have one site producing the radiotracer and transporting it to the other sites in Scotland rather than 3 or 4 sites all producing tracers. Realistically it would take 6 months of work for a radio-chemist to set up production of a new tracer and cost hundreds of thousands of pounds. You would need a relatively large number of patients to justify this e.g. all newly diagnosed GBM in Scotland. You would need a national initiative supported by CSO and universities and you would need to start with a pilot study. Both SINAPSE and SANON could help. This is a national rather than a local issue and would need a clinician to lead a group of people to develop this.

ACTION

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fMRI in Brain tumours: Clinical and future perspectives

Current clinical applications in Scotland
Avinash Kanodia (Dundee)

fMRI currently used both clinically and in research in Glasgow, Edinburgh, Dundee and Aberdeen.
Current uses:

- Lateralisation of speech centre
- Epilepsy (especially surgery)
- Tumour surgery

Funding issues. “NHS” pays in Edinburgh.

Physics and technical perspectives
Ian Cavin (Dundee)

Not all NHS boards are using fMRI.

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The technique uses "endogenous" contrast (no injection involved). How "magnetisable" are different materials in the body? Oxygenated Hb is diamagnetic and de-oxygenated is paramagnetic. Change in T2 relaxation times. BOLD – blood oxygen level dependent technology.
Mechanism: basal blood flow in the brain initially. Then a "stimulus" applied e.g. 30 seconds of hand clenching, which increases blood flow to that area of the brain and increases the MR BOLD signal which is detected by T2 imaging. fMRI detects the change in this venous blood flow. The draining vein may be distant from the exact site in the brain that it supplies.

This is rapid imaging (25-30 slices in 3 seconds). Due to the rapidity this restricts the size of voxel/resolution of the image. The signal is lost and the quality of image is less good at air/tissue interfaces e.g. sinuses. There is time differences between the image slices produced which need to be taken into account. The limit on how fast the scanner can go is due to peripheral nerve stimulation effects and potential cardiac arrhythmias induced in the patient. If you do increase resolution with smaller voxels this will lead to a higher signal to noise ratio.

Practical considerations:

- Making sure the patient understood the command for the "stimulus".
- It is possible to do "online" analysis of the images at a work station at tehe time with the Siemmens techonology.
- Other packages/software manufacturers used are SPM and FSL.
- Analysing these images involves using statistical analysis and choosing a "threshold" level of signal that you feel is significant in response to a certain stimulus.
- SPM/FSL technology is not CE marked, Siemens system is CE marked.
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Radiology perspective
Arnab Rana (Aberdeen)

fMRI in neurosurgery aims to measure neuronal firing. It does this by measuring changes in blood flow in blood vessels rather than changes in the neurons themselves i.e. a surrogate for neuronal changes. In brain tumours both the neuronal material and the blood vessels are abnormal and therefore assumptions about the use of fMRI that have been derived from its use in psychology may not always apply. The exact mediator of this neurovascular coupling is not completely understood (?Nitric oxide/lactate/arach acid). We do know that it is changes in the ratio of oxygenated to de-oxygenated blood (BOLD) that produces the MR signal because both of these states have different magnetism.

Looking at examples from psychology:
Motor activities are generally hardwired in the brain along embryological tracts and reproducible. For this reason fMRI is good for motor mapping.
Language activities are more fluid/flexible and could be better described as a network rather than one area of the brain being responsible for language. This is important when considering the use of fMRI pre-surgery when trying to understand if the area a tumour is in will affect a patient's language. It will also be affected by hemisphere dominance. It can be used to determine hemisphere dominance pre-surgery.

Disadvantages of fMRI for brain tumour imaging and in general:

- Tumour effects on blood vessels. The signal could go down rather than increase
- Helps with language lateralisation rather than localisation
- Patient selection is important – patients need good hearing, vision and cognition to co-operate with the imaging.

- Carotid stenosis can alter results
- Affected by external factors, e.g. caffeine, breathing CO2. These can also be used to improve images/as an advantage.

Neurosurgery perspective
Peter Bodkin (Aberdeen)

In GBM survival benefit is only seen when the extent of resection is over 78%. There is an increasing drive for gross tumour resection for lower grade gliomas also.

Diffusion tension imaging versus awake surgery/neurophysiological monitoring (awake or asleep). E.g. "Neuronavigation": a surgical technique whereby a reference frame is attached to the patient's head and an infra-red camera is used to produce a 3D image of where the surgeon is in space.

fMRI has better sensitivity and specificity for motor tasks than for detecting language networks in the brain.

Neurosurgical craniotomy for brain tumours can be done in the sequence awake/awake/awake (local anaesthetic); asleep/awake/asleep or asleep/awake/awake. General anaesthetic with total intravenous anaesthesia and a laryngeal mask airway rather than endotracheal tube. Video showing awake craniotomy.

Research and future perspectives
Gordon Waiter (Aberdeen)

Aberdeen have been using fMRI since 2000. Explanation of a "Cambridge/Liege" study in which fMRIw as used to detect awareness when patients were in a vegetative state.
Description of a study done in Aberdeen using MRI and FDG PET.
Future: functional connectivity imaging (resting state fMRI) in which one looks at the "off" stimulus series of images only. The brain signals will still be changing during this time. "Resting state networks" e.g. vision, language, somatomotor. This could be used in patients with GBM. Could fuse DTI PET uptake and resting state fMRI.

Discussion on opportunities for collaboration
Cyril Pernet (Edinburgh)

Making fMRI a reality:
Clinical constraints – having reliable protocols that are sensitive and specific.
Setting up a fMRI protocol:

1. Pick important things to measure with fMRI e.g. motor tasks, language, visual attention. Can do within (24 hours apart) versus between patient comparisons to test how good the imaging is. With surgical use of fMRI one is mostly looking at the "single subject" level.
2. Method of getting and assessing the images. Working out your statistical threshold level for results which will be set based on how important it is to decrease the risk of getting a false positive or a false negative result. Usually in this instance, clinically, false negatives are worse. Validation of the fMRI imaging test against the control - direct electrical stimulation (DES) which is performed by surgeons intra-operatively. Be aware that even DES can be variable (can change the gain/stimulation used).

3. Making fMRI automated/feeding the images through to the PACs system so that they can be used clinically. In Edinburgh it is possible to put the images onto PACs but some manual help is still needed to do this. If it was going to be done on a bigger scale this would need to be improved.

Outlined the need for collaboration between centres in Scotland with regards to setting up these protocols.

In order to get this up and running or use it in a clinical trial we need local clinicians to act as local PIs and interested surgeons to do the DES (optional). It could be run in SINAPSE centres. A feasibility study to harmonise protocols between centres would be needed prior to a full scale clinical trial.

ACTION

Cyril and colleagues from other centres to set-up a feasibility study looking at harmonisation of fMRI protocols

Project Updates and Discussion

<u>Optimising small animal MRI to measure invasion in glioblastoma xenografts</u>

Antoine Vallatos (Glasgow)

The aim of this project is to optimise the 7MRI imaging techniques for measuring invasion in a glioblastoma model. Techniques investigated were:-

- **Relaxation Techniques:** T2 and T2 relaxation
- **Molecular Mobility Techniques:** DW (including different scales and observation times such as b-factor), DW map, ADC and FA
- **MR Perfusion Techniques:** PCASL and DW ASL

Longitudinal studies were used over 3 months. And different imaging techniques were compared. MR techniques were also compared to histology sections stained with Ki67 (marker of cell proliferation).

Because MR sections are thicker than histological sections, work was conducted on ROI techniques for combining three histological sections. A PhD student project has started on working on clustering ROI techniques for this application.

<u>Results/Conclusions</u>

Small animal MRI techniques are now able to:

- Probe qualitative properties of GBM invasion
- Probe low tumour infiltration regions
- Detect/predict GBM invasion earlier than standard imaging techniques
- Show comparable invasion volume to histology

Ongoing work:

- Further developments on the promising ASL and DWASL techniques
- Consolidate image analysis techniques
- Develop new image analysis tools for ROI selection (e.g. clustering)
- Develop image correlation tools

<u>Development of a radiolabelled PARP inhibitor</u>

Filip Zmuda (Glasgow)

The aim of this project is to develop a molecular imaging agent that can be used to provide information on PARP inhibitor toxicity and dosing regimes.

A library of PET and SPECT imaging candidate tracers has been produced.

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In vitro evaluation has enabled selection of one PET and one SPECT lead candidate.
Radiolabelling of the lead candidates has been achieved with 18F for PET and 123I for SPECT.
Absence of a small animal scanner in Glasgow has meant that in vivo studies have progressed using ex vivo imaging.
In vivo evaluation of the SPECT candidate has shown the tracer to have a high specificity for PARP-1 in vivo.
Further studies will aim to evaluate the PET candidate in vivo.
Further studies will also look at the effect of radiation on PARP-1 expression using the PET tracer.
There was discussion of these studies and dynamic PET imaging to provide time activity curves was thought to be needed to get the best data. In addition, determination of the lead candidate's ability to cross the intact BBB was suggested.

Predicting radiation induced neurotoxicity in elderly glioblastoma patients

Greg Naylor (Glasgow). Anthony Chalmers presented in Greg Naylor's absence

Can Shelton Scale be used to access vulnerability: a retrospective study. Scheltens scale is a semi quantitative rating scale on T2 MRI. Identification of white hyperintensities/legions, size and number. Needed to be modified to exclude tumour. Hypothesis was a high score would predict a vulnerable brain and radiotherapy toxicity.
54 patients since 2007 treated with hypofractionated radiotherapy. 28 had no MRI and another 2 ruled out. 24 patients scan were given a Scheltens score and compared with survival. There was a non significant trend towards decreased survival with increased score.
Next want to perform a prospective study and use toxicity measures as a more accurate measure than survival.
This study as lead to a MD funded project on Clinical imaging and Molecular Biomarkers that predict benefit from active intervention in elderly patients. Dr Lorimer from Brighton working on this retrospective analysis. Factors that will be looked at are clinical (modified CGA), biological (MGMT, IDH1) and imaging (Scheltens score). Opportunities for additional imaging studies in a prospective study.