PHD STUDENTSHIP PROJECT PROPOSAL: BRC PROJECTS

PROJECT DETAILS	
Project Title	Maximising use of imaging data in clinical trials
Short Project Title	Maximising use of imaging data in clinical trials

SUPERVISORY TEAM	
Primary Supervisor	Professor James O'Connor (holds IRS)
Associate Supervisor(s)	Dr Nuria Porta Professor Dow-Mu Koh
Secondary Supervisor	Professor Emma Hall (holds IRS)

DIVISIONAL AFFILIATION	
Primary Division	Division of Radiotherapy and Imaging
Primary Team	Quantitative Biomedical Imaging
Site	Sutton
Other Division (if applicable)	Division of Clinical Studies
Other Team (if applicable)	ICR-CTSU

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Anatomical imaging with CT and MR is used in nearly all large phase II and phase III trials to monitor disease and determine survival endpoints such as progression-free survival (PFS), through systems such as the Response Evaluation Criteria in Solid Tumours (RECIST). RECIST measures treatment response by change in the sum of the longest diameters (SLD) of target lesions, evolution of non-target lesions (NTL), appearance of new lesions (NL) and unequivocal progression of NTL. RECIST is widely adopted as an imaging biomarker that is objective, uniform across tumour types, uniform across participating clinical trial sites and uniform across clinical trials [Litiere 2017].

Although developed for chemotherapy agents, RECIST has been validated for novel targeted agents, even when their different mode of actions do not cause obvious tumour shrinkage [Litiere2019]. However, various functional imaging methods derived from MR, PET and other modalities are used in an emerging number of studies that evaluate novel therapies, especially those that do not induce cytotoxicity or target specific molecular pathways [O'Connor 2017].

In all of these cases, spatially complex data collected at multiple time points and with potentially multiple parameter readouts are reduced to single composite measurements; individual lesions are seldom evaluated. This is despite all patients in clinical trials having multiple scan episodes and a substantial proportion having metastatic disease.

There is an unmet need to determine the optimum study design that can:

a) Track dynamic changes of single lesions over time and incorporate this into assessment of PFS
b) Use data from multiple lesions to increase the power for a given number of patients, while accounting for within-subject effects that arises from patients having multiple lesions
c) Assess the above for both anatomical (RECIST) and functional imaging biomarkers

Therefore, it is critical to understand the correlated nature of data emerging from imaging studies, and apply appropriate advanced statistical analyses.

PROJECT AIMS

1. Review existing literature methodology
2. Train in imaging trials statistical methodology (an international unmet need)
3. Develop appropriate and optimised study design for imaging trials, with focus on multiple scan data points and also for patients with multiple metastases
4. Apply the optimised designs and analyses to anatomical CT and MR data (RECIST 1.0, 1.1 measurements) and evaluate for enhanced predictive power

Apply the optimised designs to functional MR data (diffusion weighted imaging; DWI and dynamic contrast-enhanced MRI; DCE-MRI) and evaluate for enhanced predictive power

RESEARCH PROPOSAL

1. Literature review and learning advanced statistical methods as required (months 0-6)

The student will learn about current approaches to analysing imaging data in clinical trials, from anatomical-based imaging biomarkers of response accepted as key endpoints in early and late phase trials (RECIST 1.0, 1.1, PERCIST, Deauville etc.) to novel imaging biomarkers developed in the context of early phase trials (functional MR and PET). Focus will be on how data from multiple lesions within single patients undergo dimensionality reduction. Evaluation will cover all solid tumour malignancies. Findings will form the basis to the literature review.

Approval for retrospective data use will be obtained from the Trial Management Groups by Dr Porta, before the candidate starts.

2. Developing optimised imaging study designs (months 6-18)

Biomarkers derived from imaging or other techniques must undergo validation and qualification before they can be designated ‘useful tools’ to guide clinical decisions [O’Connor 2017]. Steps include:

a) Demonstration of precise and accurate measurement (technical validation);
b) Demonstration of measuring a relevant aspect of biology or predicting an outcome (biological and clinical validation)
c) Demonstration of altering ‘clinical decision making’ (qualification)

Imaging studies have different research questions at each domain, and therefore, different study designs with specific endpoints are required.

A characteristic feature of imaging studies is the different sources of within-patient variation (e.g. multiple scans over time per patient; multiple lesions per patient; multiple readers per scan). This is particularly present in technical validation studies, where different performance characteristics can be estimated: bias, repeatability, reproducibility or agreement with a reference standard or with another method [Obuchowski 2019]. A common framework to analyse data derived from technical validation studies are multilevel models (also known as hierarchical or mixed effects models) [Demidenko 2013]. Sample size

determination in multilevel designs requires attention to the fact that statistical power depends on the total sample sizes for each level [Snijders 2005].

The student will develop a common framework for design and sample size calculation of imaging studies for technical performance assessment to facilitate its used amongst the imaging research community. It is envisaged that a new package in the statistical software R (https://cran.r-project.org/), or potentially a web-based application in its Shiny package (https://shiny.rstudio.com/) will be developed.

3. Applying optimised designs and analyses to RECIST 1.0, 1.1 data (months 18-30)

Despite having a breadth of data generated to monitor RECIST response (SLD, NTL, NL) at multiple time points over time, the data are usually summarised into a binary outcome (objective response or not, at a specific time point) or time-to-event endpoint PFS. Further insight into the anti-tumour activity of a novel treatment can be explored by better understanding the dynamics of tumour change, not only in overall tumour burden, but also in per lesion characteristics and size over time. Disease at metastatic stages is highly heterogeneous, and differential responses to novel targeted agents have been observed in different lesions of the same patient. By identifying the lesion or group of lesions that drive final prognosis we hypothesise developing more personalized interventions in future trials.

RECIST was developed for use as primary endpoint in the context of early phase trials. These trials are designed with high power to discard novel agents that do not show enough activity, and only progress into further development those agents that show promising activity. This approach ignores the tumour dynamics up to the time of response, focusing only on a binary endpoint for its go/no-go decision. Novel designs incorporating tumour dynamics to improve power of phase II trials with objective response rate as primary endpoint have been proposed [Wason 2013], but its practical implementation is yet to be seen.

There are statistical methods to jointly model the dynamics of tumour burden (e.g. per-lesion size) together with survival data (e.g. overall survival). These range from the initial approach of the RECIST working group using extensions to the Cox model such as time-dependent covariates and landmark analyses [An 2015], to a more appropriate way to incorporate the variability of the tumour burden measurements via multivariate joint frailty models for longitudinal and survival data [Krol 2018]. The latter makes use of all available data and can be more efficient, but it can be computationally intense to estimate, and its prediction performance suffers from misspecification of the tumour kinetics model [Halabi 2019]. Functional data analysis, a nonparametric framework, has been recently proposed in this context for modelling nonlinear longitudinal processes [Yan 2017].

The student will apply and extend the above advanced statistical methods to data from ICR-CTSU trials. We have identified 10 ICR-CTSU clinical trials in advanced disease whose primary or key secondary endpoints include objective response rate as defined by RECIST criteria 1.0 or 1.1, measured by regular radiological assessments (CT/MRI) while patient was on treatment and up to disease progression. Trials (with data collected) include 9 phase II trials (2 chemotherapy, 2 hormone therapy, 5 targeted agents) and 1 phase III trial (chemotherapy), cover different disease areas (2 breast, 2 prostate, 2 penis, 1 gynae, 3 rare), and encompass around 875 patients with at least one measurable lesion. Access to the trials data held at ICR-CTSU will be with the permission of the respective Trial Management Groups.

4. Applying optimised designs and analyses to functional DWI and DCE-MRI data (months 30-42)

The same optimised methods from the above sections will be employed in functional imaging data. These studies are data rich but this poses challenges in how optimum parameters may be selected without introducing further statistical challenges through excessive dimensionality. Study will begin in two related bevacizumab studies with combined N=65 patients with 2-8 liver metastases from colorectal cancer. Parameters derived include ADC, T_1, $IAUC_{60}$, K^{trans}, v_e and v_p at double baseline and 48hr, d7,

d14 (extended Tofts model, individual AIFs) and subsequent time points following treatment with bevacizumab monotherapy [Jayson 2018] (EudraCT 2009-011377-33).

The same methods will be tested in two further independent datasets, courtesy of Dr Kyrre Emblem (Oslo University). These are:

a) Breast cancer metastases to brain (N=40, acquired at Dana Faber and Massachusetts General Hospital in Boston, MA patients have 1-9 measurable metastases treated with bevacizumab, with DWI and DCE-MRI parameters at baseline, 24hr and 7 weeks). PFS and OS are available as clinical endpoints (Clinicaltrials.gov identifier: NCT01004172)
b) Lung and melanoma metastases to brain (N=80, acquired at Oslo University Hospital, patients have multiple metastases, with DWI, DSC-MRI and vessel size imaging parameters at baseline then every 3 months). PFS and OS as clinical endpoints (Clinicaltrials.gov identifier: NCT03458455)

5. Thesis writing and submission (months 42-48)

The student will collate published data and other material into their thesis, guided by the supervisory team. This will in part be from data written up into at least 2 original peer review high impact journals.

LITERATURE REFERENCES

- An M-W, Han Y, Meyers JP, Bogaerts J, Sargent DJ, Mandrekar SJ. Clinical Utility of Metrics Based on Tumor Measurements in Phase II Trials to Predict Overall Survival Outcomes in Phase III Trials by Using Resampling Methods. Journal of Clinical Oncology. 2015;33(34):4048-4057.
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- Halabi S, Li C, Luo S. Developing and Validating Risk Assessment Models of Clinical Outcomes in Modern Oncology. JCO Precision Oncology. 2019;3.
- Jayson GC, Zhou C, Backen A, et al. Plasma Tie2 is a Tumour Vascular Response Biomarker for VEGF inhibitors: Evidence for a Multi-Compartment Model for Cancer Treatment. Nature Communications. 2018;9: 4672.
- Król A, Tournigand C, Michiels S, Rondeau V. Multivariate joint frailty model for the analysis of nonlinear tumor kinetics and dynamic predictions of death. Statistics in Medicine. 2018;37(13):2148-2161.
- Litière S, Collette S, de Vries EGE, Seymour L, Bogaerts J. RECIST — learning from the past to build the future. Nature Reviews Clinical Oncology. 2017;14(3):187-192.
- Litière S, Isaac G, De Vries EGE, et al. RECIST 1.1 for Response Evaluation Apply Not Only to Chemotherapy-Treated Patients But Also to Targeted Cancer Agents: A Pooled Database Analysis. Journal of Clinical Oncology. 2019;37(13):1102-1110.
- Obuchowski NA, Mozley PD, Matthews D, Buckler A, Bullen J, Jackson E. Statistical Considerations for Planning Clinical Trials with Quantitative Imaging Biomarkers. Journal of the National Cancer Institute. 2019;111(1):19-26.
- O'Connor JP, Aboagye EO, Adams JE, et al. Imaging biomarker roadmap for cancer studies. Nature Reviews Clinical Oncology. 2017;14(3):169-186.
- Snijders, T.A.B. Power and Sample Size in Multilevel Linear Models. In: Encyclopedia of Statistics in Behavioral Science. Vol Volume 3. Chicester: Wiley; 2005:1570–1573.
- Wason JMS, Seaman SR. Using continuous data on tumour measurements to improve inference in phase II cancer studies. Statistics in Medicine. 2013;20:4639-4650.
- Yan F, Lin X, Huang X. Dynamic prediction of disease progression for leukemia patients by functional principal component analysis of longitudinal expression levels of an oncogene. Annals of Applied Statistics 2017;11(3):1649-1670.

CANDIDATE PROFILE	
Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)	
Pre-requisite qualifications of applicants	BSc or equivalent in computer science, mathematics, medical statistics, or similar subject
Intended learning outcomes	1. Experience of conducting comprehensive literature review 2. Knowledge of current use of imaging in clinical trials and the pitfalls of these approaches 3. In depth experience of data simulation, mathematical modelling and advanced statistical methods and their implementation in software such as *R* or *STATA* 4. Knowledge and experience in the design and execution of data science experiments 5. Experience in writing up data into peer reviewed accepted publications 6. Understand the clinical setting of early phase cancer trials and practical challenges that are often encountered 7. Experience working collaboratively with radiologists, clinicians and scientists in a highly interdisciplinary environment, and will benefit further from interaction with external leading experts in the field.
ADVERTISING DETAILS	
Project suitable for a student with a background in	☐ Biological Sciences ☐ Physics or Engineering ☐ Chemistry ☑ Maths, Statistics or Epidemiology ☑ Computer Science ☐ Other (provide details)
Keywords	1. Imaging Biomarkers
	2. Cancer Clinical Trials
	3. Statistical modelling
	4. Maths or statistics PhD London
	5. Correlated data
	6.