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Editorial

RAPPER — A Success Story for Collaborative Translational Radiotherapy Research

N.G. Burnet *†, G.C. Barnett ‡, H.R. Summersgill *†, A.M. Dunning §, C.M.L. West *†

* Division of Cancer Sciences, University of Manchester, Manchester Cancer Research Centre, Manchester Academic Health Science Centre, Manchester, UK
† The Christie NHS Foundation Trust, Manchester, UK
‡ Oncology Centre, Addenbrooke's Hospital, Cambridge, UK
§ University of Cambridge Department of Oncology, Strangeways Research Laboratory, Cambridge, UK

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RAPPER (Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy) is a success story for national collaborative translational science. The study was established with the aim of identifying genetic variants associated with a patient's risk of developing radiotherapy side-effects that could be combined in a clinical test incorporating non-genetic risk factors to individualise treatment [1]. Underpinned by hypothesis-driven science, RAPPER collects blood to extract germline DNA from patients with high-quality clinical outcome data – collected mainly in national trials led by members of the UK clinical oncology community. It is an effort that we, as a community, should be very proud of. This editorial provides an update on the status of RAPPER and its future ambitions.

Current State of the RAPPER Resource

The UK clinical oncology community via RAPPER has collected specimens with linked clinical outcome data from just over 10 000 patients, making it the largest such resource in the world. Figure 1 highlights successful national recruitment into RAPPER and summarises the status of the resource, with a breakdown by tumour type. Most patients recruited to RAPPER were treated within the context of quality-controlled clinical trials, with a small proportion from single investigator-led studies. Our approach means that the quality of the linked clinical, treatment and outcome data is higher than possible in routine clinical work. RAPPER has also been very cost-effective, as all the clinical data were collected mainly under the auspices of the relevant clinical studies. RAPPER has recruited from 83 hospitals (54 radiotherapy centres) and is currently open at 79 hospitals (54 radiotherapy centres).

RAPPER Raised the Quality of Radiogenomics Studies

RAPPER drove the founding of the international Radiogenomics Consortium (RGC), an international collaboration involving 131 institutions in 33 countries [3]. The RAPPER team introduced genetic epidemiology expertise and experience in genome-wide association studies (GWAS) that raised the quality of radiogenomics studies and contributed to the development of best-practice methodology. One of our first papers highlighted the limitations of the early radiogenomics studies and raised awareness of the small effect sizes expected for single nucleotide polymorphisms (SNPs) and the need for combining cohorts to ensure studies are adequately powered [4]. Our methodology developments included an approach for deriving a standardised total average toxicity (STAT) score to facilitate pooling data across cohorts and countries [5]. RAPPER also contributed to establishing STROGAR guidelines for reporting radiogenomics studies that emphasise the need for power calculations and multivariable analyses [6]. RAPPER genotyping data have been used in key publications that have identified SNPs associated with the risk of radiotherapy side-effects. Most of these have been international collaborative efforts involving members of the RGC, which shows the value of collaborative working, particularly when large studies are needed to validate risk SNPs for radiotherapy toxicity [7–9].

Author for correspondence: N.G. Burnet, The University of Manchester, 3rd Floor, Proton Beam Therapy Centre, Oak Road, Manchester, M20 4BX, UK. Tel.: +44-161-306-8465.
E-mail address: neil.burnet@manchester.ac.uk (N.G. Burnet).

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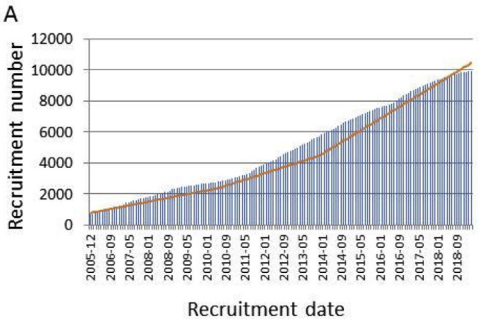

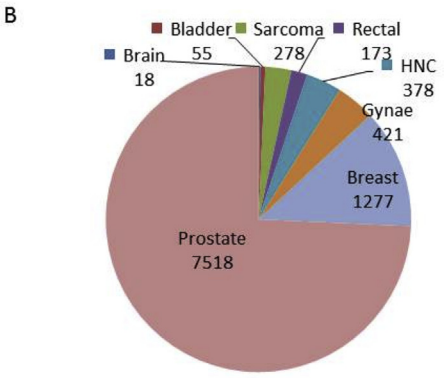

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Tumour	Trial	Recruited	DNA	Genotyped
Bladder	HYBRID	2	2	
	RAIDER	53	20	
Brain	HIPPO	4	4	
	VOXTOX	14	7	
Breast	Cambridge IMRT	1052	1052	966
	Prosp Breast	225	208	88
Gynae	PRECIOUS	11	11	
	Prosp Gynae	171	135	
	Cervix lymphocyte	207		
	GI care	7	7	
	Retro Gynae	25	25	
H&N	ART-DECO	178	166	
	COMPARE	10	2	
	DARS	16	6	
	DE-ESCALATE	87	86	
	VOXTOX	87	52	
Prostate	CHHIP	529	528	353
	CHHIP 3	1947	1946	1657
	DELINEATE	133	120	
	Dose Esc	58	58	2
	HDR Brachy	538	514	
	IMRT	6	5	
	PACE	420	404	
	PATCH	51	48	
	Pelvic IMRT	288	287	16
	PIVOTAL & BOOST	133	106	4
	POPS	3	2	
	PRECIOUS	12	12	
	PROCON	19	18	
	Prosp Prostate	497	443	
	RADICALS	1283	1263	327
	RT01	266	266	255
	STAMPEDE	1311	1244	
	VOXTOX	24	23	
Rectal	EXCITE	76	76	57
	RICE	97	97	30
Sarcoma	IMRIS	72	69	
	VORTEX	206	206	164
Total		10118	9518	3319

Fig 1. Current status of the RAPPER cohort. (A) Graph showing cumulative actual versus target recruitment. Note that the study had accrued just over 700 samples as it opened from the Cambridge Breast Intensity-modulated Radiotherapy Study [2], which had been established with this translational component in mind. (B) Tumour treatment site breakdown of 10 118 samples collected up to January 2019. (C) Samples and data generated per trial.

RAPPER Contributes to Increased Understanding of the Genetics of Radiation Toxicity

A key publication in 2007 identified five SNPs associated with the risk of breast cancer [10]. Four of these were in genes that would not have been obvious candidates; the fifth lay in a 'gene desert'. The paper confirmed the need to use GWAS methodology to identify genetic variants that could not be predicted *a priori*. This approach has been vindicated by the subsequent success of RAPPER and RGC GWAS, which are identifying additional, novel radiosensitivity loci within genes not previously known to be involved in the cellular or tissue response to radiation. The new variants identified lie in or near genes involved in normal tissue function [11–13]. Many of the common genetic variants identified seem to be tissue-specific, which provides a challenge for understanding the full spectrum of toxicities associated with radiotherapy to different tumour sites. RAPPER has also investigated the common genetic variation associated with an increased predisposition to cancer. This has had an important outcome in excluding a link between a high genetic cancer predisposition and increased risk of toxicity in the adult population [14,15]. Of course, there may be different considerations in children.

Future Plans for Genetic Analyses

The success of the work to date has highlighted that continuing efforts are worthwhile and will identify a larger number of variants [16]. These variants could be combined as a polygenic risk score and included with relevant patient and treatment factors to provide clinical models of risk. In order to develop these models, maximising the signal to noise ratio is essential, and detailed dose information should include the delivered rather than the planned dose where possible [17]. Hopefully, these risk models will be exploitable in the future as a test to individualise treatment.

Efforts to identify more variants are ongoing. RAPPER contributes nearly a third of the ~30 000 patients with multiple cancer types identified within the RGC as having GWAS and linked radiotherapy toxicity data. The greatest efforts to date have been on prostate cancer. A group within the RGC is now focusing on head and neck cancer and RAPPER hopes to contribute data for a planned meta-analysis (see Figure 1 for a summary of the RAPPER head and neck cohorts). We also recently genotyped our rectal cancer and sarcoma patient cohorts and analyses are planned in these groups. The latter will be included in an RGC meta-analysis of up to ~30 000 patients planned for 2019 to identify SNPs associated with acute toxicity across tumour types.

Current RGC GWAS exclude individuals with non-European ancestry to minimise confounding due to population sub-structure effects. Differences in allele frequencies and admixture (presence of DNA in an individual from a distantly related population or species) in different ethnic groups and subgroups can result in frequent false-positive results and reduce statistical power. As the size of our cohorts increases it will be possible to test risk SNPs identified in patients with European ancestry in other ethnic groups that were excluded from published studies.

Expanding RAPPER to Collect Samples from Patients having Proton Treatment

Research to date involved patients treated with photons and there is a need to expand efforts to patients treated with particle beam therapies. The recently completed RGC meta-analysis of prostate cancer patients included about 500 prostate cancer patients treated with carbon ions (in Japan), but there is a need to expand the number of cohorts of patients treated with particle beam therapies, especially protons. The latter would underpin the identification of genetic differences that might differentially affect the development of toxicity after, for example, photons versus protons. 'RAPPER proton' will start in 2019, to collect clinical data and DNA from all patients treated with protons at the Christie Hospital. It is hoped that this initiative can eventually be expanded nationally.

A Success Story for Collaborative Radiotherapy Research in the UK

The success of RAPPER is due to the support of the UK clinical oncology community. This support has led to the largest single collection of DNA samples with linked radiotherapy clinical and toxicity data in the world and this has allowed us to influence scientific progress in radiogenomics. The finding of genetic variants that are definitively linked with differences in toxicity is close to clinical application. Approaches to changing patients' treatment have been discussed over a long period [18,19]. Risk models incorporating genetic data could be used to divide patients into 'sensitive' (10%), 'normal' (50%) and 'resistant' (40%) groups to provide an initial step to individualising treatment [18,19]. Potential strategies to mitigate toxicity in the sensitive group would be tumour type-dependent, e.g. hyperfractionation, use of proton beam therapy in place of X-rays, limiting the total radiotherapy dose with additional chemotherapy, or surgery in place of radiotherapy. Drug treatments to abrogate toxicity could be investigated in an enriched population of those most likely to benefit. For the resistant 40%, simple dose escalation, especially by increasing the dose per fraction, or with a more definitive hypofractionated schedule, could be explored. Thus, patients at both ends of the spectrum of normal tissue radiosensitivity will probably benefit. However, further refinement of a genetic 'signature' and its combination with patient- and treatment-related factors is still necessary, so deployment to the clinic remains a few years away.

The success of RAPPER represents an example of what is possible in translational research, driven by a desire to improve the outcome of patients requiring radiotherapy, when the community embraces the collaboration.

Conflicts of Interests

The authors declare no conflict of interest.

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