ALPHA DART

Using alpha particles to treat solid tumours

A team from Cambridge looks at setting up Diffusing Alpha-emitters Radiation Therapy (Alpha DaRT) for Vulva Cancer.

Carcinoma of the vulva is rare. It makes up just 3–5% of gynaecological cancers and generally occurs in the elderly. Most are squamous cell carcinoma (85–90%). The current treatment option is surgery, often followed by concurrent chemo-radiotherapy. There is high morbidity associated with radiotherapy. Acute toxicity of radiotherapy has been reported by van Triest et al in 2021.

- Skin ≥ Grade 2 92%
- Skin ≥ Grade 3 54%
- Pain ≥ Grade 3 37%

Emerging evidence from a new study published by the Alpha Tau Medical team using alpha particles – Alpha DaRT – was of significant interest to try to improve the options for patients with vulva cancer. The potential benefits being:

- To downstage the primary with minimal morbidity resulting in less extensive (or no) surgery
- To improve local control
- Abscopal effect on distant disease (nodes/metastases)
- Less post-operative radiotherapy and associated morbidity.

Alpha particles are known to be very destructive to tumour cells. They cause direct, irreparable damage to the cell DNA and lead to cell death. However, the range of alpha particles in tissue is very limited. Therefore, until now, it was not possible to use alpha particles as a locally delivered treatment for solid tumours.

Technology and technique

The Alpha DaRT technology relies on the diffusion of atoms that emit alpha particles within the tumour tissue, in order to overcome the short-range limitation of the alpha particles themselves. The extended range that the alpha radiation can reach enables the potential treatment of the entire tumour.

Alpha DaRT technology is based on small quantities of Radium-224 (^{224}Ra) affixed to metal sources that are inserted directly into the tumour. When ^{224}Ra decays, it releases further radioactive progeny with short half-lives that diffuse through the tumour. These atoms emit additional short-range alpha radiation that damages and kills cancer cells within a short period of time.

The surgical insertion technique:

- The Alpha DaRT source is made of stainless steel
- The ^{224}Ra is embedded on the source surface
- The Alpha DaRT sources are strung on a biocompatible suture.

Alpha needle applicators are used to place sources. Fixation of the suture at the skin surface is simple and fast.

The distribution of radioactive atoms inside the tumor has direct correlation with the necrotic areas they cause.

A feasibility study for 10 patients at Cambridge University Hospitals NHS Foundation Trust (CUH), with the primary end-point being tolerability (treatment completed as planned) was accepted by the MHRA in March 2023. The first clinical patient was treated in May 2023.

Radiation safety, regulatory compliance and commissioning

There are a number of novel aspects to Alpha DaRT that impact on its introduction into clinical use from a physics perspective.

Alpha DaRT starts as a sealed source device and is only considered unsealed once applied inside the tumour, when the radioactive progeny are able to diffuse. While the methodology of inserting the applicators is similar to a brachytherapy technique, the mechanism of action of DaRT is completely distinct from that of brachytherapy.

"THESE ATOMS EMIT SHORT-RANGE ALPHA RADIATION THAT DAMAGES AND KILLS CANCER CELLS"

Therefore, clinical introduction required the involvement of three teams of medical physicists:

Radiation protection to ensure compliance with UK regulations.

Nuclear medicine to provide expertise on unsealed source therapy: radioassay of the applicators and patient blood and urine samples, and systems of control for theatre and ward.

Radiotherapy to provide expertise on brachytherapy and commissioning and planning using alpha dosimetry.

It was important for us all to first understand the physics of the decay scheme of the DaRT sources.

The ^{224}Ra is produced in a ^{228}Th generator. No ^{228}Th is present in the ^{224}Ra sources.

^{220}Rn is a short-lived gas, so highly dispersible. Depending on the trajectory of the emitted alpha particle, either ^{220}Rn, ^{216}Po or ^{212}Pb daughters can "escape" from surface of source. As the half-lives of the progeny are much shorter than that of ^{224}Ra, the daughter products remain in secular equilibrium with ^{224}Ra. The only significant half-life in the decay chain is that of ^{212}Pb (10.6 hrs). Once daughters are released from the source into the body, ^{212}Pb therefore becomes the head of the decay chain and is the dominant radionuclide in any samples such as blood and urine. The radioactive progeny emit a range of α, β and γ radiation, so contamination is readily detectable.

Regulatory compliance

Radiation protection physicists began the process of ensuring compliance with UK regulations for this first application of Alpha DaRT in the UK. There are three sets of regulations applicable to the introduction of DaRT: the Environmental Permitting Regulations 2016 (EPR16), the Ionising Radiations Regulations 2017 (IRR17) and the Ionising Radiation (Medical Exposure) Regulations 2017 (IRMER17).

EPR16 governs the keeping and use of radioactive material and the accumulation and disposal of radioactive waste, with the aim to protect the public and the environment from hazards associated with radioactive material/waste. EPR permits are issued for sealed and unsealed sources.

IMAGES: SHUTTERSTOCK

EPR16 actions specific to DaRT were identified as:

Source designation: Alpha Tau ships the sources in airtight applicators, as *sealed sources*. They become *unsealed sources* when removed from applicators. Agreement was obtained from the Environment Agency (EA) that designation should be in accordance with the CUH *unsealed* EPR permit.

The CUH permit's "any other" category for holding radioactive material prior to and during source use allows up 6 GBq of miscellaneous radionuclides. Nuclear medicine had already allocated 4 GBq of this for ^{223}Ra, ^{75}Se and ^{125}I. This left adequate capacity for ^{224}Ra. The shipment of sources for the first clinical patient totalled 191 sources, and a total of less than 30 MBq.

The CUH permit allows for the accumulation of solid waste (unused applicators, removed sources and contaminated items) to decay for a maximum of 14 days for up to 100 GBq of ^{212}Pb ($T_{1/2}$ = 10.6 hours) and six months for up to 10 GBq of ^{224}Ra ($T_{1/2}$ = 3.6 days). In practice, two months is sufficient to ensure all ^{224}Ra products have become inert.

If ^{224}Ra from opened applicators is present in the waste, it must be stored in water in an airtight container to contain any potentially dispersible ^{220}Rn. Unopened, spare applicators are considered sealed, hence can be stored to decay without water. If ^{224}Ra is not present, it is stored as ^{212}Pb and there is no risk from ^{220}Rn.

Patient urine contains ^{212}Pb and its daughters, but should not contain any ^{224}Ra. As ^{212}Pb is a beta emitter, this aqueous waste is managed under the *Any Other Beta* allowance of 2 GBq per month.

Nuclear medicine uses IPEM excretion factors for common diagnostic and therapeutic radiopharmaceuticals. Factors depend on the radiopharmaceutical and patient physiology, and can be determined analytically and/or experimentally.

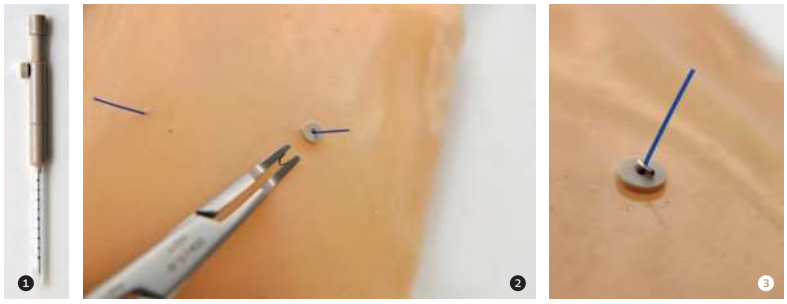
It was necessary to determine a conservative estimate of the excretion factor from Alpha Tau data, and then seek EA approval because ^{224}Ra / ^{212}Pb excretion factors are not included in the IPEM list. Using a default of 100% would have caused issues, due to the already high environmental impact on the CUH site from ^{177}Lu, ^{223}Ra and ^{131}I therapies.

Based on the analytic methodology used initially, a very conservative figure of 4% was agreed with the EA:

Fraction of ^{212}Pb excreted in urine	=	Administered ^{224}Ra activity A_0	*	probability decay will result in ^{212}Pb atom escaping source [0.6] f_d	*	probability ^{212}Pb leaks from tumour into blood stream [0.6] f_t	*	probability of ^{212}Pb transferring from blood plasma into urine

This was confirmed with subsequent Alpha Tau

Figure ❶ An Alpha DaRT needle applicator. **Figure ❷** Suture in situ under the skin
Figure ❸ Fixation of the suture at the skin surface using micro clips and buttons



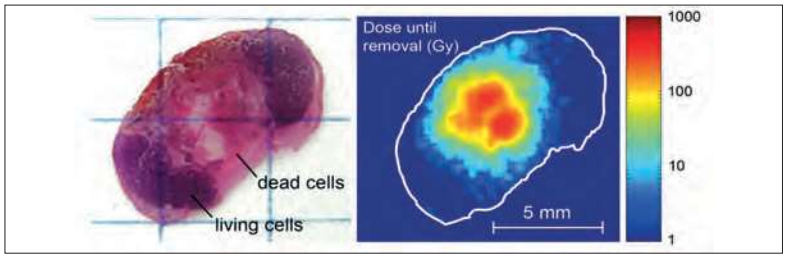


Figure ❹ (left) Hematoxylin-eosin (H&E) stained 5µm section taken from a SCC tumor treated with a 224Ra Alpha DaRT source. Darker (purple) regions in are composed of viable cells, lighter (pink) regions are necrotic. (right) The radiation pattern of the same section. (Lior Arazi and Tomer Cooks – courtesy of Alpha Tau)

Figure ❺ The ^{224}Ra decay chain. Data taken from the NuDat3 database website

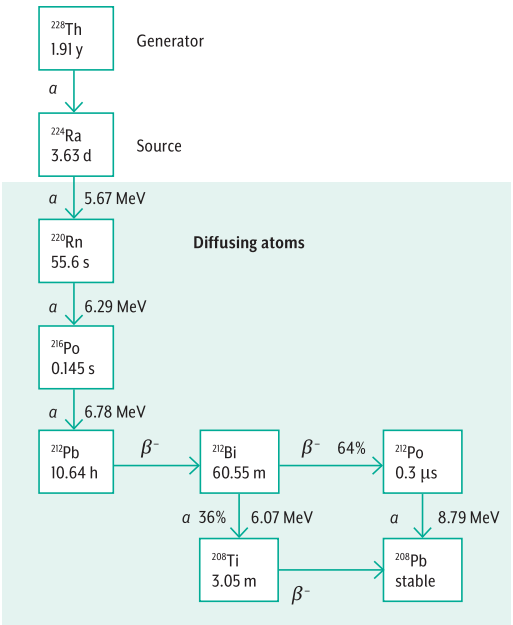


Figure ❻ The radioassay calibration jig and applicator holder

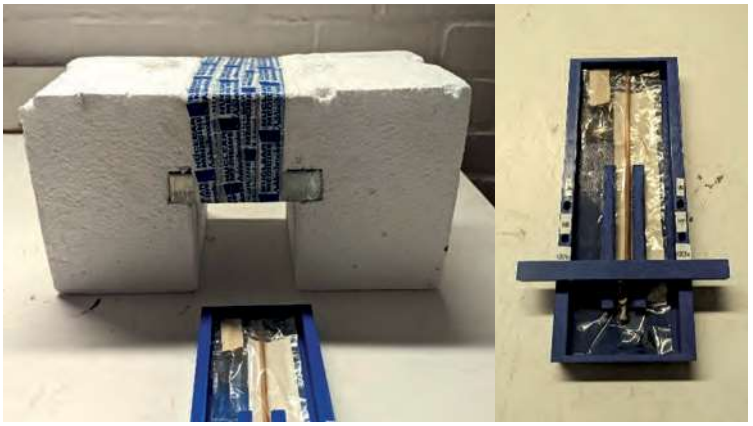
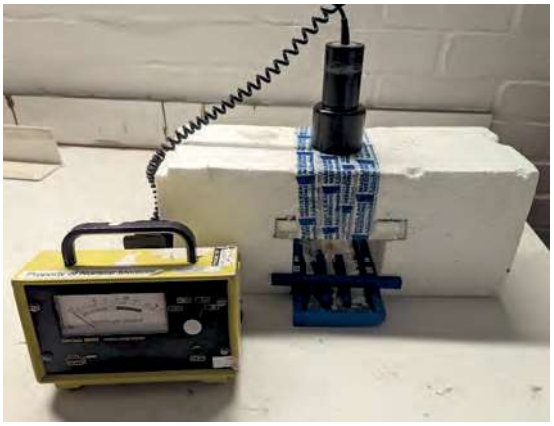


Figure ❼ Monitor set-up for the radioassay calibration jig



experimental data from urine measurements, estimating 0.005 kBq ^{212}Pb per litre of urine per kBq of ^{224}Ra inserted to the tumour. Assuming 1–2 litres of urine output per day, this is 0.5–1%.

IRR17 governs all work with ionising radiation, including work in high-radon areas, with the aim to minimise radiation exposures to staff and public.

IRR17 actions specific to DaRT were identified as:

- Confirmation that HSE consent for radioactive administrations were already in place for nuclear medicine and brachytherapy.
- Radiation risk assessments identified a number of action points: that local rules with RPSs were required, that some staff monitoring was required, that theatre should be designated a controlled area until post-implant/removal monitoring confirms no lost sources or contamination present. Contamination monitoring to be performed using alpha and gamma detectors. During their hospital stay, in-patients should be kept in a side room with en suite and designated as controlled areas. In-patient hospitalisation is not always required and appropriate radiation advice will be given to patients returning home.

Specific contingencies were identified which required contingency plans referenced in the local rules. These included sources coming loose, spills of patient blood and urine, lost sources, and sources left inside the patient following the removal procedure.

IR(ME)R17 governs exposures of ionising radiation associated with medical uses including research, and aims to optimise radiation exposure to patients and volunteers.

IR(ME)R17 actions specific to DaRT were identified:

- Ethics approval was obtained for the Participant Information Sheet.
- ARSAC study approval, with CUH as sponsor.
- ARSAC employer licence for CUH updated to specify "^{224}Ra-148-149 ^{224}Ra seeds for the Treatment of Squamous Cell Carcinoma of the Vulva".
- ARSAC practitioner licence updated to include the study.
- Confirmation that appropriate IRMER employer's procedures were in place in radiotherapy.

Commissioning for clinical use

With regulatory permissions in place, commissioning could proceed. This involved:

- Calibration for the radioassay of applicators.
- Calibration for the radioassay of patient samples.
- Commissioning the planning system.

Radioassay of applicators: Applicators are calibrated prior to delivery. They arrive encased in sterile plastic packaging that should not be opened prior to use in theatre. Hence, the local assay is not a definitive calibration. The aim is to verify that the activity received matches the label to within a reasonable tolerance, i.e. that the number of sources indicated is correct. This is done by measuring the gamma

"IRR17 GOVERNS ALL WORK WITH IONISING RADIATION, INCLUDING WORK IN HIGH-RADON AREAS

emissions: ^{224}Ra: 241 keV (4.1%) and ^{212}Pb: 239 keV (43.6%).

To calibrate the radioassay system, three applicators containing one, three and six sources were measured and a plot of cps vs kBq was drawn. This was repeated for all available contamination monitors. The plot equation was used to verify applicator activity prior to implantation.

Radioassay of patient blood and urine samples: Patient blood and urine are assessed for radioactivity during the treatment period. Data from other DaRT trials indicated activity concentrations in the Bq/g range that were suitable for measurement in a local sample counter. As ^{212}Pb has a short half life (10.6 hours), it is not possible to obtain a calibration source of pure ^{212}Pb. The assay method is to use a ^{224}Ra source and calculate how much ^{212}Pb there is. Alpha Tau provided a sealed calibration source in resin.

The calibration source reached secular equilibrium (*equal amounts of ^{224}Ra and ^{212}Pb*), such that:

$A_{212Pb} = 1.138 \times A_{224Ra}$

The calibration source has an accurate ^{224}Ra activity, allowing calculation of ^{212}Pb activity [Bq]

The relationship between ^{224}Ra activity and detected cps:

$CPS_{224Ra} = [0.041 + (0.435 \times 1.138)] \times A_{224Ra} \times \epsilon_{detection}$

where 0.041, 0.435 = branching fractions (^{224}Ra for 241 keV, ^{212}Pb 239 keV γ respectively)

$\epsilon_{detection}$ = detection efficiency [cps/radioactive disintegrations per sec]

Count ^{224}Ra source to find $\epsilon_{detection}$

For a sample containing only ^{212}Pb, the relationship would be:

$CPS_{212Pb} = 0.435 \times A_{212Pb} \times \epsilon_{detection}$

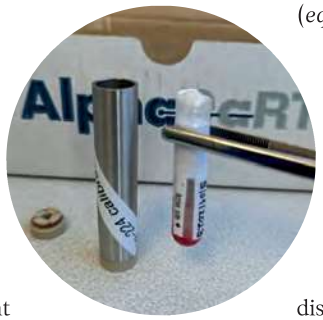


Figure ❽ Sealed calibration source ^{224}Ra in resin

By using the detection efficiency and the CPS of the measured source, one can extract the activity of ^{212}Pb. Then, the conversion factor from CPS to Bq can be easily inferred (CPS measured divided by the calculated ^{212}Pb activity).

Commissioning the MIM Symphony Alpha DaRT planning system: In order to commission any treatment planning system (TPS) comparison should be made between the performance of the TPS with measured data, with known uncertainties associated with the measured data and with assessed inaccuracies in the planning algorithm. The performance is then assessed relative to criteria of acceptance, i.e. limits of accuracy. It is necessary to observe and record under what conditions the system is acceptable or not acceptable (specifically for DaRT, this requires assessing cold spots).

The dosimetry of a brachytherapy planning system generally relies on TG-43 formalism.

However, for DaRT alpha particles this formalism does not make sense for multiple reasons: There is no TG43 data for alpha-particles; A decay constant (with exponential decay of the dose-rate) cannot be applied for the alpha-sources with various decay products. Reference air kerma Rate (RAKR) which is numerically identical to the air-kerma strength 1 U = 1 μGym^2/h = 1 cGycm^2/h with a reference point, usually referred to 1m from the source, is impractical for DaRT treatment, as the dose is negligible there.

The DaRT tumour dose model was adapted to the TG43 formalism and incorporated into the MIM software. The details of how the DaRT model was cast into the TG43 formalism will be described in a separate future publication by Alpha Tau.

Commissioning of the planning system dosimetry, therefore, relied not on checking TG43 data, but on validation of the MIM axial and radial profile output against published data.

Figure ❾ Tests specific to brachytherapy, Table 4.4 IPEM81

Test	Range	Analysis
A. Source data		
Basic source data	(a) **Activity**	**Comparison** against manufacturers and published data
	(b) **Air kerma**	
	(c) **Tissue attenuation** and scatter factors	
	(d) **Half-life**	
B. Point doses and distributions		
	(a) **Single source**	**Dose or dose rate** along a line normal to the axis of the source at distances from centre of the source or sources of 0.5, 1.0, 2.0, 5.0, 7.0 cm. Dose distribution compared with publiched distributions
	(b) **Multiple sources**	
	(c) Standard source arrangements e.g. Manchester, Paris,dosimetry	
C. Source reconstruction		
Phantom with dummy sources	(a) **6 line sources**	**End-point coordinates** and source length
	(b) 12 seed/pellets	
	Manual and auto matching	
D. Coordinate translation and rotation		
	(a) **Sagittal and coronal planes**	Dose distributions compared with published distribution. Repeat of test B (oblique plane only)
	(b) 30° oblique plane through a source inclined at 30° to the normal plane in test B	

Figure ❿ Plot to determine equation activity measured by Alpha Tau @ implant time (kBq) vs counts measured in site detector calibration jig.

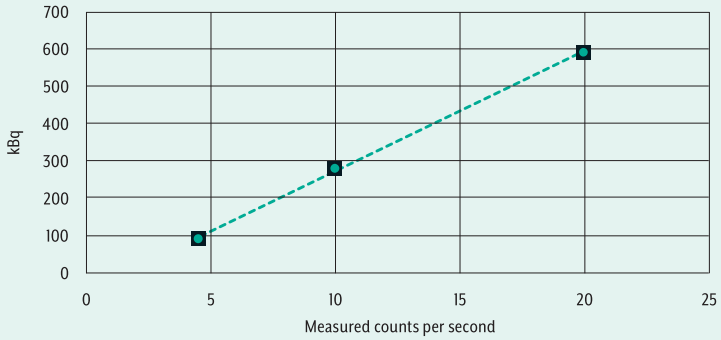


Figure ⓫ MIM treatment planning system versus COSMOL, radial profiles.

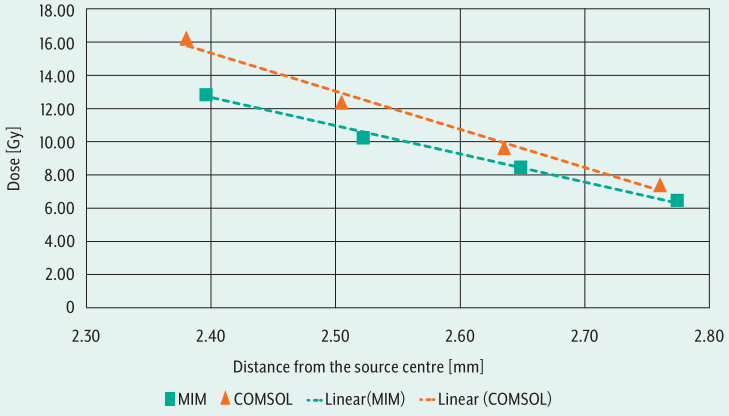
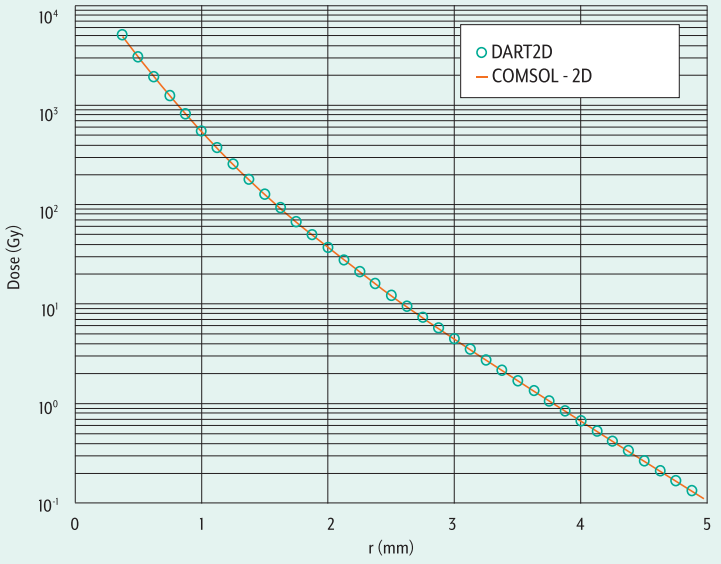


Figure ⓬ Total alpha particle dose calculated using DART2D and a 2D calculation in COMSOL MultiphysicsTM for the high-diffusion "lead-dominated" case.



Dose resolution and 10 Gy norm point

Distance of the 10 Gy point from the source centre was calculated using 1D data profiles from MIM with distances normalised to match 1 Gy point in COMSOL (radial profile). A 2nd order polynomial fit to 4 points around 10 Gy was applied and solved to estimate the 10 Gy point :

The calculated values for 10 Gy point (distance from the source centre) are MIM 2.53 mm and COSMOL 2.60 mm. The 1D line source dose calculation in MIM begins at the centre of the source – assuming the "surface" is located at the centre (origin is at r=0), whereas Heger *et al.* Med Phys 22 takes into account the actual source's radius (r=0.35 mm).

The current status of the dosimetry as presented in MIM therefore provides a slight underestimation of the spatial distribution of the dose in comparison to the latest 2D calculations. In practice, the dose overlap we apply is thus clinically slightly higher, providing us extra clinical reassurance that we will not have cold spots.

Results and conclusion

The first patient was recruited to the DaRT feasibility study for vulva cancer and successfully treated at CUH May 2023.

GTV ~3.5 cc and CTV~13.3 cc were outlined on diagnostic MR. 141 DaRT sources were inserted in theatre. The treatment plan was produced on CT, fused to MR and indicated excellent dose coverage to the GTV on Day 0, V100 =89%, D90 = 95% (9.5Gy), and minimal cold spot 0.06 ml, not deemed to be clinically significant.

Repeat CT planning on day 7 showed improved coverage with the reduction of postoperative oedema GTV V100 =97%, D90 ~200 % (20 Gy). No cold spots were identified.

Initial clinical response is very encouraging.

The newness of this technology and its first use in the UK and in the vulva gave the CUH physics team an exciting challenge. We hope we have now forged a path and identified a safe and comprehensive set-up method that will make it an easy and straightforward task for other UK centres to emulate.

***Dr Sarah Heard**, Head of Nuclear Medicine Physics; **Evelyn Shin**, Senior Nuclear Medicine Physicist; **Graham Whish**, Lead Clinical Scientist-Radiation Protection; **Diane Whitney**, Head of Brachytherapy Physics; **Dr Magdalena Klodowska**, Radiotherapy Physicist; **Dr Li Tee Tan**, Consultant Clinical Oncologist. All are based at Cambridge University Hospitals NHS Foundation Trust.*

For further information on DaRT and its implementation, visit bit.ly/DaRT