Patient-specific QA using 4D Monte Carlo phase space predictions and EPID dosimetry

I A Popescu1, 2, P Atwal1, J Lobo3, J Lucido3 and B M C McCurdy4
1British Columbia Cancer Agency, Vancouver, BC, Canada
2University of British Columbia, Vancouver, BC, Canada
3University of Colorado School of Medicine, Denver, CO, USA
4CancerCare Manitoba and University of Manitoba, Winnipeg, MB, Canada

E-mail: tpopescu@bccancer.bc.ca

Abstract. The goal of this review is to outline a solution for patient-specific QA of VMAT, IMRT, and other complex treatment delivery techniques. This solution has been developed in direct response to clinical needs, in order to allow our institution to offer VMAT to all patients who could potentially benefit from this advanced technique. To date, over 2500 VMAT patient plans and approximately 1000 IMRT patient plans have been verified by this method in Vancouver, while 40 other institutions worldwide have expressed interest in, or are already at various stages of implementing, this process. The addition of EPID in vivo dosimetry (i.e. data acquired during the patient treatment) and associated Monte Carlo predictions amounts to introducing a ‘measurement component’ in this QA process, which is currently mandated by the regulatory framework in some European countries, or for billing purposes in the USA. The fully automated, patient-specific, Monte Carlo based QA process described here is fast, maximally efficient in terms of departmental resources, and capable of simulating any plan in a single run, regardless of its complexity.

1. Introduction

From a quality-assurance and patient-safety perspective, the fundamental question is how to optimally use clinical resources in order to make available to patients the best radiation therapy techniques at our disposal, in a safe and accurate manner. A closely related question is whether our current QA practices can safeguard patients from radiotherapy incidents, such as the ‘New York incident’ [1], to give one example. Needless to say, this is a topic of great interest for the European (ESTRO), American (AAPM and ASTRO) and Canadian (COMP and CARO) organizations of radiotherapy practitioners, as well as for individual radiotherapy institutions worldwide. While it has to be recognized that pre-treatment VMAT QA is currently a clinical mainstay, we believe that an increasing focus on comprehensive critical-event and failure-mode analysis of the entire radiotherapy chain is more likely to prevent adverse clinical events.

During our more than a decade-long experience with the QA of IMRT and VMAT plans, our practice has gradually evolved from pre-treatment phantom-measurement QA for each patient plan towards a three-component procedure consisting of (1) independent 3D dose recalculation using Monte Carlo for each plan, with a full pre-treatment phantom measurement for every 50th plan (which currently occurs approximately once a week); (2) an increasingly comprehensive routine linac QA procedure, with emphasis on dynamic MLC, dynamic gantry, and variable dose rate tests; and (3)
monitoring of dynalog/trajectory-log files acquired during patient treatment, with the option of rerunning the Monte Carlo dose calculation with these inputs. The fully automated Monte Carlo based QA process outlined in this paper has accumulated an extensive clinical track record, with over 2500 VMAT patient plans verified by this method in Vancouver and several hundred others worldwide. The core of this process is ‘source 20’ of DOSXYZnrc, developed by Lobo and Popescu [2, 3], for 4D Monte Carlo simulations of continuously-variable beam configurations, with arbitrary degrees of freedom. It would have been impossible to offer this advanced treatment to all patients who could have potentially benefited from it without a streamlined QA procedure that involved physics resources at a level commensurate with the clinical workload. One of the benefits of this process being automated is that the user is not required to be a specialist in Monte Carlo applications. The possibility of a user error is also eliminated by automation. This QA process has been applied to a variety of clinical cases, including jaw-tracking, non-coplanar, and multiple-arc VMAT, for both standard and flattening filter free (FFF) photon beams.

A quality-assurance protocol deserving of the ‘patient-specific’ title should be relevant to the actual patient treatment and be capable of providing \textit{in vivo} dosimetry. Moreover, such a QA method should ideally be able to alert incidents such as the one quoted above. The major current commercially-available QA solutions, such as ArcCHECK, MapCheck, and EPIdose (Sun Nuclear, USA); Delta4 (ScandiDos, Sweden); Octavius (PTW Freiburg GmbH, Germany); or MatriXX (IBA Dosimetry GmbH, Germany), are valuable within the pre-treatment paradigm, but would not be able to catch an egregious error during treatment, such as patient mis-positioning, missing MLC, etc. In contrast, patient 3D dose calculation using real-time linac log information or transmission portal EPID dosimetry and cone-beam CT imaging to assess changes in patient anatomy, could give practitioners the data required for adaptive patient dose accumulation over the entire course of treatment and for inferring the associated radiobiological consequences. To this end, we have recently introduced the capability of simultaneously providing dose deposition in both the patient CT data set and any type of planar (entrance or exit) detector for VMAT Monte Carlo QA [4]. By enabling DOSXYZnrc to optionally output a 4D IAEA phase space during a source 20 simulation, it is now possible to collect the particles exiting the patient during a VMAT simulation. This phase space can be used for further synchronized simulations of EPID dose or images, either globally, incrementally, or per control point, allowing comparisons of the 4D phase space EPID prediction with the actual EPID data acquired with the patient on treatment.

2. Materials and methods

2.1 General considerations

Our Monte Carlo simulations use several recent developments of source 20, which were introduced in order to address specific challenges presented by TrueBeam (Varian Medical Systems, USA) simulations, namely the unavailability of a full linac model and the fact that input IAEA phase spaces may be non-planar. Some of these new features have been already included in the 2013 release (V4-2.4.0) of the BEAMnrc/DOSXYZnrc system (National Research Council, Canada) [5, 6], while others will be incorporated into the next release. The TrueBeam simulations used input phase spaces provided by the manufacturer and independently validated by several groups (for example, for the 6X FFF phase space, see the experimental validations by Gете et al [7] and more extensively – by Belosi et al [8]). The number of histories for each simulation was selected such that the statistical uncertainty in the high dose voxels (PTV) was approximately 1%. The Monte Carlo simulation results were converted to absolute dose for the planned number of monitor units using the formalism of Popescu et al [9], with an amended methodology required for TrueBeam [10]. A detailed description of our Monte Carlo simulation parameters can be found in [3] and [9]. The patient treatment and verification plans were generated by the Eclipse (Varian Medical Systems, USA) treatment planning system (TPS), using AAA version 11.0.31.
2.2 Automated Monte Carlo workflow

Various components of the general process outlined here have been validated and presented in previous publications (in chronological order: [11, 9, 12, 2, 13, 3, 14, 15, 4, 16], as the system evolved over the last decade. At the pre-treatment QA stage, the input for the process consists of DICOM files exported from the TPS. In its current clinical version, the process is initiated by typing a command representing essentially the patient’s hospital ID and no further user intervention is required. In an alternative version, which is used in a different institution, even this initial step is removed and replaced by a daemon-based monitoring of exported DICOM files. In that case, the process is automatically initiated once the presence of such files is detected. At treatment stage, we have developed the capability of taking into account linac log files (dynalog files for the Varian iX and related series and trajectory-log files for TrueBeam) as inputs for a secondary, post-delivery, Monte Carlo simulation. The flowchart of the process is shown in figure 1.

![Flowchart](image)

**Figure 1.** The main components of the automated Monte Carlo QA process.

2.2.1 Object recognition and process selection

The main input into the process is the DICOM RP plan file exported from the TPS. The scripts scan this file to determine whether the plan is for an iX (and related Varian Clinac series) or for a TrueBeam linac, the treatment unit identifier for the case of unmatched linacs, the type of MLC (Millennium or HDMLC), fluence type (standard or FFF beam), and any other characteristics that require specific input parameters. The export of the TPS DICOM RD total dose file is also expected, since it is overwritten in the end with the Monte Carlo dose. This allows the import of the Monte Carlo dose back into the TPS for in-depth comparisons with the planned dose, taking advantage of existing TPS tools, such as dose-volume histograms, plan comparison, dose subtraction, etc. If these are the only two files exported from a verification plan, the simulation will be performed by default on the corresponding verification phantom. Otherwise, if the set of CT DICOM files is also exported, the script will automatically detect that and use ctcreate to generate a patient-specific phantom for the simulation.

2.2.2 ‘DICOM-to-egsinp’

Once the process selection step is completed as described above, the script generates a single BEAMnrc egsinp file and a single DOSXYZnrc egsinp files, regardless of the number of fields in the plan. This step takes into account the transformation between the DICOM and DOSXYZnrc coordinate systems. Several other auxiliary files required for the post-processing step are generated at this time. We have used in the past a DICOM dictionary provided by the in-house code [17], but several other users have employed the open-source Python-based code [18]. We are also in the process of migrating towards the Python-based solution, since we believe that an open-source,
publicly-available and supported code is preferable to an in-house one, for a variety of reasons, including the fact that other users could reproduce and independently verify the work carried out in our institution.

2.2.3 BEAMnrc and DOSXYZnrc
Our BEAMnrc simulations employ the SYNC* suite of component modules [5], allowing full flexibility of treating any plan as having jaw-tracking (whether it is actual dynamic jaw tracking or step-and-shoot style jaw setting specific to a multiple-field plan with different field sizes). Likewise, dynamic and/or step-and-shoot MLC for single or multiple-field plans is treated as a single dynamic MLC sequence. By employing the SYNC* modules, it is possible to use any BEAMnrc accelerator either as a shared library called by DOSXYZnrc at run time, or as a stand-alone executable. In the former case, no intermediate phase spaces are required. In the latter case, 4D IAEA phase spaces can be scored, preserving the full properties of beam particles, including the MU index, which allows for further synchronized simulations. For reasons partly historical and partly related to simulation speed, we collect a 4D IAEA phase space file under the SYNCJAWS module, which becomes the input for the downstream simulations. However, no further downstream phase spaces need to be collected, regardless of the plan complexity.

2.2.4 DICOM Monte Carlo dose and 4D exit phase space
Upon completion of the simulation, we apply a 3D locally adaptive Savitzky-Golay denoising filter [19] to the raw Monte Carlo dose, following the methodology introduced by Kawrakow [20]. A detailed description of the role of this filter in the context of our system can be found in [16]. The resulting dose distribution is then converted to absolute dose (in Gy), as mentioned in subsection 2.1, and cast in DICOM RD format, which allows import into the planning system. Optionally, a 4D IAEA phase space is output by DOSXYZnrc. The geometry of this phase space is that of the parallelepiped boundary of the patient CT phantom. The time-like dimension is provided by the MU index variable scored for each particle. This phase space can be scored in either BEAMnrc or DOSXYZnrc coordinate systems.

2.2.5 EPID ‘cine-mode’ prediction
When a 4D IAEA exit phase space is scored in the BEAMnrc coordinate system, it is straightforward to perform a synchronous simulation into an EPID phantom, since the EPID is static in this coordinate system, even for multiple-field non-coplanar VMAT plans. Such a simulation takes only a few minutes on our computer cluster, for one billion histories, since particles in the 4D exit phase space only have to travel a few centimetres in air before being incident on the EPID phantom. A single simulation is again required in all cases, without the need to build a phantom for each patient-EPID relative position, as we did in our earlier work [4]. As a by-product, simulations of cone-beam CT image acquisition and associated patient dose are also possible using the exit phase space. We have introduced a MU filter in source 20 that rejects particles outside a user-defined MU index interval. This filter is enabled by including two new optional variables defining the lower and upper limits of a MU index interval in the egsinp file. This feature can be used to calculate integral, incremental, or per control point, dose distributions either in the patient CT phantom, or in the EPID.

2.2.6 Dynalog/Trajectory-log input
We have developed the capability of generating Monte Carlo input files for post-delivery dose recalculation based on linac log files, namely ‘dynalog files’ [12, 13], for the Varian iX and Clinac series and ‘trajectory-log’ files for TrueBeam (unpublished). The information contained in these files is much more detailed than that in the DICOM RP file, resulting in Monte Carlo input files with up to approximately $3 \times 10^7$ control points. These files can be collected for every treatment fraction and reflect the performance of various dynamic linac components during the actual beam delivery.
2.2.7 Robustness and continuity checks

In the main script there are two instances (when running BEAMnrc and DOSXYZnrc) when the simulation is divided into a user-selected number of ‘jobs’ distributed to processors. This is done using the HTCondor (University of Wisconsin - Madison, USA) high-throughput distributed parallelization software, which allows for concurrent job allocation and dynamic resource management. In order to have a robust automated system, we implemented checks wherein HTCondor is queried to ensure that the jobs are running as expected. The first in the sequentially numbered set of distributed jobs creates a ‘lock file’, which all jobs in the task must access, one at a time, to determine how many particles are left to simulate and thus when the distributed simulation is complete. During the BEAMnrc simulation, each job creates an empty phase space file at the outset into which the resultant particle information is written. The script checks periodically if both the lock file and the phase space file for the first job exist. While the lock file exists, the script remains in a while-loop in which it periodically checks the status of the lock file. The lock file will be deleted by the last job to complete. Once the script determines that the lock file ceased to exist, it is assumed that the distributed task has completed successfully. If, however, either the lock file or the first job’s phase space file do not exist, then the status of the first job is checked. There is a particular tag for this status, which must read ‘R’ for a running job. This status tag is checked periodically in a while-loop, until it reads ‘R’. Within this loop the next thing to check is whether the status tag is set to any value at all or if it is empty. If it is not empty, then we assume that the job is in the process of being started, or it is idle while waiting in the HTCondor queue, and nothing further is done but to ‘sleep’ a few seconds and recheck the tag. On the other hand, if the status tag is found to be empty at this point, then the job can be assumed to be complete, but this fact must be verified. The script breaks out of the while-loop at this point and executes the code already mentioned regarding checks for the lock file. After determining that the BEAMnrc run has completed successfully, the phase spaces produced by each individual job are combined, an egslst file is generated (which contains the monitor chamber backscattered dose information required for the absolute dose conversion), and the script moves on to the DOSXYZnrc simulation. The DOSXYZnrc distributed simulation is checked in a similar fashion, except that each job creates a phase space file only if the option to generate a 4D IAEA exit phase space has been selected. In both instances, once it is determined that the task distribution has been completed successfully, any jobs for the given task which are still on the queue running (or to be run) are considered to be so-called ‘orphaned’ jobs and are deleted to ensure maximum availability of computing resources. After the end of the DOSXYZnrc simulation, the patient/phantom 3ddose is subjected to the post-processing steps described in 2.2.4, while the 4D exit phase space is used for the EPID simulation as mentioned in 2.2.5.

3. Results

Experimental validations of our Monte Carlo system, using ionization chambers, films, TLD in an anthropomorphic phantom, EPID, and the ArcCHECK system, have been previously published or reported at conferences (e.g. [4, 7, 11, 13, 16]). Of the independent validations performed at other institutions, the longest series has recently been reported by Cronholm et al [21] (unpublished). This group performed comparisons between Monte Carlo dose calculations using source 20 and the Delta4 system for a total of 100 clinical TrueBeam VMAT plans (30 plans with 6 MV beams and 70 plans with 10 MV beams). They concluded that the Delta4 measurements were generally in better agreement with the Monte Carlo than with the Eclipse computed dose distributions. The measurements were compared with MC and TPS results using a 3D gamma analysis based on a 3%/2mm criterion, with a lower cut-off of 20% of the maximum dose. The average and median pass-rates for MC were 97.7% and 98.1%, respectively.

In order to illustrate the versatility of our QA system, we present two clinical cases that have been encountered in our practice. Although they are different in terms of treatment techniques, they were both treated from the point of view of our MC QA system in the same way, namely as single-field treatments with multiple variable degrees of freedom.
The first case is of a patient who received treatment in both lungs simultaneously, for bilateral tumours. Each site was treated with two arcs, resulting in a four-arc VMAT plan with two isocentres, as shown in figure 2, with the field properties given in table 1.

![Figure 2](image)

**Figure 2.** 4-arc, 2-isocentre, VMAT beam arrangement for a bilateral lung treatment, simulated as a ‘single field’ in source 20.

| Field ID | Machine/Energy | Gantry | Collimator | Couch | MU |
|----------|----------------|--------|------------|-------|----|
| VMAT 1   | TrueBeam 6 MV  | 0 ccw 181 | 45 | 0 | 2611 |
| VMAT 2   | TrueBeam 6 MV  | 181 cw 0 | 315 | 0 | 2643 |
| VMAT 3   | TrueBeam 6 MV  | 179 ccw 0 | 45 | 0 | 2068 |
| VMAT 4   | TrueBeam 6 MV  | 0 cw 179 | 315 | 0 | 2052 |

| X1 jaw | X2 jaw | Y1 jaw | Y2 jaw | x_iso | y_iso | z_iso |
|--------|--------|--------|--------|-------|-------|-------|
| 2.1    | 3.0    | 2.2    | 2.8    | -7.00 | 0.00  | 0.00  |
| 2.8    | 2.2    | 2.1    | 3.0    | -7.00 | 0.00  | 0.00  |
| 3.7    | 3.2    | 3.7    | 3.1    | 7.00  | 1.00  | -2.50 |
| 3.1    | 3.7    | 3.7    | 3.2    | 7.00  | 1.00  | -2.50 |

There were 9374.71 MU for the combined four fields. A single source 20 egsinp file was required for this simulation, containing 392 control points that defined the four partial arcs of this plan. Table 2 gives the beginning and the end of the control point sequence. On each line, the numbers represent the following variables: the \((x, y, z)\) coordinates of the isocentre; the spherical coordinate angles defining the beam direction in the DOSXYZnrc coordinate system, \(\theta\) and \(\phi\); the rotation angle about the beam axis, \(\text{phicol}\); a variable with the role of \(d_{\text{source}}\), which, in the case of a IAEA phase space input, is computed for each particle using the distance between the isocentre and the origin of the BEAMnrc coordinate system (typically, the linac SAD) and the \(z\) coordinate of the particle, as scored in the IAEA phase space - thus, it is this distance (SAD) that has to be specified in the egsinp file; and, finally, the fractional monitor units delivered up to this control point, \(MU\_index\).
Table 2. The first three and last three of the 392 control points, as written in the DOSXYZnrc egsinp file for the simulation of the plan shown in figure 2.

| Control Points | X1  | X2  | Y1  | Y2  | Z   | MU  | Energy | Angle | Distance |
|----------------|-----|-----|-----|-----|-----|-----|--------|-------|----------|
| -7.24, -28.27, -87.887, 90, 270.00, 225, 100.0, 0.0000 |       |     |     |     |     |     |        |       |          |
| -7.24, -28.27, -87.887, 90, 269.07, 225, 100.0, 0.0000 |       |     |     |     |     |     |        |       |          |
| -7.24, -28.27, -87.887, 90, 267.20, 225, 100.0, 0.0000 |       |     |     |     |     |     |        |       |          |

An axial slice through a cylindrical-phantom Monte Carlo vs. Eclipse dose comparison is shown in figure 3.

Figure 3. Monte Carlo dose (left panel) and Eclipse dose (right panel) for a cylindrical-phantom verification plan corresponding to the plan shown in figure 2. The 3D gamma agreement was 99.0%.

The second case is an 8-field, non-coplanar, 3D-conformal SBRT lung plan, with a combined 11877.76 MU over 4 fractions, corresponding to a SBRT prescription of 48 Gy. They were all small fields, with a maximum jaw setting of X1 = 1.4 cm, X2 = 1.3 cm, Y1 = 1.2 cm, and Y2 = 1.3 cm. The field arrangement is shown in figure 4.

Figure 4. Non-coplanar field arrangement for an 8-field 3D-conformal SBRT lung plan.
Figure 5 shows an axial slice through the Monte Carlo vs. Eclipse dose comparison on the patient CT, while figure 6 shows a DVH comparison for the 4DCT-generated ITV and two organs-at-risk.

![Figure 5. Monte Carlo dose (left panel) and Eclipse dose (right panel) for the plan shown in Figure 4, on the axial slice containing the isocentre.](image)

![Figure 6. DVH comparison between Monte Carlo and Eclipse dose distributions, for selected structures, for the plan shown in Figure 4.](image)

Finally, figure 7 shows Monte Carlo predicted and EPID measured transmission doses for selected control points for a prostate VMAT plan. These images are formed by radiation transmitted through the patient body and our system has the capability of simultaneously providing the dose in the patient CT phantom (not shown here, but see [4] for details), as explained in subsections 2.2.4-5 above.

4. Conclusion and future directions

Our decade-long, thousand-case, pre-treatment QA measurement (ionization chamber and film) experience supports the idea that there is no additional patient-safety benefit from measurement based QA over Monte Carlo based QA, when a rigorous, failure-mode-analysis inspired, linac QA protocol is implemented along with dynalog or trajectory-log data monitoring and in vivo EPID dosimetry comparisons with the Monte Carlo 4D phase space predictions. By accumulating the patient dose delivered during the entire course of treatment (possibly in an adaptive manner, in conjunction with in vivo CBCT data), this process represents an authentic ‘patient-specific QA’ and could gradually replace the pre-treatment phantom-based QA process that an institution would typically use in the early stages of its VMAT program. We are also aware of the availability of at least one commercial solution that offers in vivo EPID dosimetry, EPIgray (DOSIsoft, France).
Since the main source of potential variability of the dose distribution over the course of a fractionated treatment is the change in patient anatomy, a significant amount of work still has to be done on adaptive Monte Carlo dose accumulation, which will allow the monitoring of realization of planning constraints (on PTV and OAR) as dose accumulates over all fractions of the treatment. This requires recalculations on updated patient geometry, as provided by CT registration with CBCT imaging. A variety of commercial software tools have the potential of accomplishing this task, such as MIM (MIM Software Inc, USA), SmartAdapt (Varian Medical Systems, USA), or VelocityAI (Velocity Medical Solutions, USA). Eiland et al [22] analyzed the geometric and dosimetric performance of a deformable registration algorithm by comparing the CBCT-registered and deformed CT set with the actual rescan of the patient at some stage of the treatment. This group found that, in spite of certain variation in volume and dose between the two CT sets, the differences were within clinically acceptable limits for most of the patients.

The Monte Carlo based QA solution presented here is freely available upon request, in open-source format, and is distributed under a GNU General Public License. Source 20 of DOSXYZnrc and the SYNC® component modules of BEAMnrc are in the public domain, as part of the standard distribution of these codes. They are also freely available in open-source format and are distributed under a specific NRC license.

5. Acknowledgements
I would like to acknowledge the contributions of Ganiyu Asuni, Alanah Bergman, Karl Bush, Conor Shaw, Tony Teke, Ernest Tsang, and Sergei Zavgorodni, who have developed various elements of the Monte Carlo based QA process described here and with whom we have had many useful discussions. We also acknowledge the work of Fujio Araki, Rickard Cronholm, Jarkko Ojala, and Lixin Zhan, who have performed extensive independent validations of source 20 in their respective institutions. The first author would like to particularly acknowledge Wayne Beckham, who - many years ago, at a time of still insufficient computing resources - envisioned the main lines of this QA process and strongly supported the effort for its construction, for the benefit of patients and staff physicists alike.

6. References
[1] Bogdanich W 2010 Radiation Offers New Cures, and Ways to Do Harm The New York Times
(http://www.nytimes.com/2010/01/24/health/24radiation.html?pagewanted=all&_r=0)

[2] Popescu I A and Lobo J 2007 Radiother. Oncol. 84 S76

[3] Lobo J and Popescu I A 2010 Phys. Med. Biol. 55 4431-43

[4] Asuni G et al 2013 A Monte Carlo tool for evaluating VMAT and DIMRT treatment deliveries including planar detectors Phys. Med. Biol. 58 3535-50

[5] Rogers D W O et al 2013 BEAMnrc Users Manual Report PIRS-0509(A)revL, National Research Council of Canada, Ottawa.

[6] Walters B et al 2013 DOSXYZnrc Users Manual Report PIRS-794, National Research Council of Canada, Ottawa.

[7] Gete E et al 2013 Med. Phys. 40 021707

[8] Belosi M F et al 2014 Med. Phys. 41 051707

[9] Popescu I A et al 2005 Phys. Med. Biol. 50 3375-92

[10] Popescu I A et al 2014. 56th Annual Meeting of AAPM, July 2014, Austin, Texas, USA

[11] Popescu I A et al 2004 Radiother. Oncol. 73 (Suppl. 1) S87

[12] Popescu I A et al 2006 IFMBE Proceedings 14 1801

[13] Teke T et al 2010 Med. Phys. 37 116-23

[14] Teke T et al 2011 Phys. Med. Biol. 56 N295-305

[15] Moiseenko V et al 2013 Phys. Med. Biol. 58 7107-16

[16] Bergman A et al 2014 J. App. Clin. Med. Phys. 15 148-63

[17] Locke C and Zavgorodni S 2008 Australas. Phys. Eng. Sci. Med. 31 290-99

[18] Mason D 2011 Pydicom: a pure python package for working with DICOM files (http://pypi.python.org/pypi/pydicom)

[19] Savitzky A and Golay M J E 1964 Anal. Chem. 36 1627-39

[20] Kawrakow I 2002 Phys. Med. Biol. 47 3087-103

[21] Cronholm R 2014 private communication

[22] Eiland R B et al 2014 J. Rad. Res. doi:10.1093/jrr/rru044 (advance access, June 6, 2014)