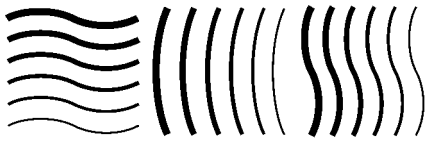
Radiation dosimetry: balance between safety and cure

Proceedings Sixth NCS Lustrum Symposium

Leiden, The Netherlands, October 5, 2012

NEDERLANDSE COMMISSIE VOOR STRALINGSDOSIMETRIE



Netherlands Commission on Radiation Dosimetry
October 2012

Preface

The Netherlands Commission on Radiation Dosimetry (Nederlandse Commissie voor Stralingsdosimetrie, NCS) was officially established on September 3rd, 1982 with the aim of promoting the appropriate use of dosimetry of ionising radiation both for scientific research and for practical applications. The NCS is chaired by a board of scientists, installed upon the suggestion of the supporting societies, including the Netherlands Society for Radiotherapy and Oncology (Nederlandse Vereniging voor Radiotherapie en Oncologie), the Dutch Society of Nuclear Medicine (Nederlandse Vereniging voor Nucleaire Geneeskunde), the Dutch Society for Medical Physics (Nederlandse Vereniging voor Klinische Fysica), the Netherlands Radiobiological Society (Nederlandse Vereniging voor Radiobiologie), the Netherlands Society for Radiological Protection (Nederlandse Vereniging voor Stralingshygiëne), the Dutch Society for Medical Imaging and Radiotherapy (Nederlandse Vereniging Medische Beeldvorming en Radiotherapie), the Radiological Society of The Netherlands (Nederlandse Vereniging voor Radiologie), the Belgian Hospital Physicists Association (Belgische Vereniging voor Ziekenhuisfysici / Société Belge des Physiciens des Hôpitaux), and and the Dutch society of technicians and other specialists in the field of medical physics (Nederlandse Vereniging van Klinisch Fysisch Medewerkers).

To pursue its aims, the NCS accomplishes the following tasks: participation in dosimetry standardisation and promotion of dosimetry intercomparisons, drafting of dosimetry protocols, collection and evaluation of physical data related to dosimetry. Furthermore, the commission shall maintain or establish links with national and international organizations concerned with ionising radiation and promulgate information on new developments in the field of radiation dosimetry.

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NCS, Delft, The Netherlands

For more information on NCS Reports, see http://www.radiationdosimetry.org

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Foreword

On September the 3rd, 1982, the Nederlandse Commissie voor stralingsdosimetrie (NCS, Netherlands Commission on Radiation Dosimetry) was established, aiming to promote appropriate use of dosimetry of ionizing radiation, both for scientific and clinical purposes. Over the last thirty years, the NCS has published 21 reports, mostly concerning dosimetry in medicine. These reports have been highly appreciated in the field of radiation dosimetry in Belgium and the Netherlands, but also further abroad. The Board of the NCS aims to keep its reports up to date and relevant for professional users.

Apart from these activities, the NCS has revitalized the NCS platform to discuss practical aspects of the implementation of European law and regulations in clinical practice with the Dutch government.

This is exactly where the NCS stands for: practical guidelines that can be used by professionals, carefully weighting the balance between accuracy and precision on the one hand and time, money and effort on the other. Keeping in mind that this balance remains important, the subject of today's symposium is "Radiation dosimetry: balance between safety and cure". To broaden our horizons, we spiced up the theme with topics that may not be within the realm of most professional's daily experience.

I wish you all a pleasant and stimulating day.

On behalf of the Board of the NCS,

Jeroen van de Kamer

Diagnostische referentieniveaus

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Het begrip diagnostisch referentieniveau vindt zijn oorsprong begin jaren negentig in het Verenigd Koninkrijk. Metingen wezen uit dat er grote variaties waren in de blootstelling aan straling bij het doen van diagnostisch röntgenonderzoek zoals röntgenfoto's in verschillende ziekenhuizen. In sommige ziekenhuizen werd zelfs teveel röntgenstraling gebruikt. Om ongewenst hoge doses röntgenstraling bij diagnostiek te voorkomen werd het diagnostisch referentieniveau ingevoerd.Het diagnostisch referentieniveau (of kortweg DRN) is de dosiswaarde die bij een routineonderzoek van een gemiddelde patiënt niet zou moeten worden overschreden.

Overschrijding van het DRN moet een motivatie zijn tot optimalisatie van het röntgenonderzoek. Toetsing door ziekenhuizen aan de DRN's droeg ertoe bij dat de stralingsbelasting bij röntgenonderzoek in het Verenigd Koninkrijk daalde. Het concept van de diagnostische referentieniveaus bleek waardevol en heeft zijn weg gevonden naar de Europese en Nederlandse wet- en regelgeving.

Een projectgroep van de Nederlandse Commissie voor Stralingsdosimetrie (NCS) met deskundigen uit het werkgebied van medisch diagnostische stralingstoepassingen heeft op verzoek van het Ministerie van VWS DRN's voor Nederland vastgesteld. Onlangs werden twee eerste publicaties van de projectgroep samengenomen tot een afsluitend rapport. De betrokken beroepsgroepen, waaronder ook de NVKF, werden bij de totstandkoming van dit rapport geconsulteerd. Het is de bedoeling dat de DRN's een plaats krijgen binnen kwaliteitsborgingsystemen van ziekenhuizen.

De overhandiging van het rapport door Jeroen van de Kamer (voorzitter NCS) aan Hugo Hurts (Directeur Geneesmiddelen en Medische technologie, ministerie van VWS) vond plaats op 11 juli 2012. In het rapport zijn diagnostische referentieniveaus beschreven voor zeven diagnostische verrichtingen bij volwassenen: mammografie, CTA-thorax, CT-abdomen, X-thorax en X-abdomen, diagnostische CT coronaire angiografie en diagnostische conventionele coronaire angiografie. Daarnaast zijn er DRN's gedefinieerd voor 4 verrichtingen bij kinderen: X-thorax, X-bekken, CT–hoofd en Mictie Cysto-Urethrogram. Deze verrichtingen zijn een goede afspiegeling van de diagnostische verrichtingen met röntgenstraling binnen de Radiologie in Nederland.

Dosimetrie in de Nederlandse borstkankerscreening

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In de Nederlandse borstkankerscreening worden gezonde vrouwen blootgesteld aan röntgenstraling om tumoren in een vroeg stadium te detecteren (screenen). De basis van screenen is het principe dat de gemiddelde grootte van gedetecteerde tumoren kleiner is bij deelname aan screening dan in de diagnostische situatie, waardoor een grotere kans op overleving voor de deelnemende vrouwen bestaat. De keerzijde van het screenen is het blootstellen van een in principe gezonde populatie aan röntgenstraling, met de potentie op inductie van tumoren.

Om tot een risicoschatting te komen in de borstkankerscreening wordt als maat de geabsorbeerde dosis in het klierweefsel bepaald, de glandulaire dosis. De afschatting hiervan gebeurd met behulp van het dosismodel van Dance. In dit model wordt een standaard borst gebruikt, bestaande uit een homogene mix van klier- en vetweefsel omgeven door een 5 mm dikke vetlaag waarmee de huid gesimuleerd wordt. De dikte van de mix aan klier- en vetweefsel en de verhouding klier- en vetweefsel hangt af van de dikte van de borst, die beschouwd wordt.

Het model van Dance gaat uit van een gemeten intree Air Kerma van de borst en het gebruik van conversietabellen om deze om te rekenen naar een glandulaire dosis. Hierbij worden een g-factor (de omrekeningsfactor naar glandulaire dosis bij een standaard röntgenspectrum en borstcompositie), een c-factor (de correctiefactor voor verschillen in borstcompositie) en een s-factor (de correctiefactoren voor verschillen in röntgenspectrum) gebruikt. Recent is het dosismodel aangepast voor de tomosynthese techniek, die momenteel reeds in enkele ziekenhuizen gebruikt wordt. Hiervoor zijn t-factoren en T-factoren in het borstmodel ingevoerd.

Naast de uitleg over het dosismodel van Dance zal de samenhang van de berekende dosiswaarden met behulp van gesimuleerde standaard borsten vergeleken worden met gemeten patiënt/cliënt dosimetrie data.

Literatuur:

Dance DR (1990), Monte Carlo calculation of conversion factors for the estimation of mean glandular breast dose, Phys.Med.Biol., vol. 35, no. 9, pp. 1211-1219.

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In-vivo dosimetry in brachytherapy: techniques and rationale

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Introduction remarks

There is a phrase by George Mallory when he was asked 'Why do you want to climb Mt. Everest?'. His answer was simple and became famous: 'Because it is there…'. This citation is used here, as it seems to this author in the context of the contribution to this NCS meeting that quite often investigators have published papers in which they describe the use of new technology for certain applications with a similar motivation: because they just had it and were looking for a purpose. A rationale is then easily found: but only afterwards. At least a number of papers dealing with in-vivo dosimetry in brachytherapy fall into this category. Basic questions such as: 'What do we want to know?' and therefore: 'What do we want/need to measure?' are often raised rather late in the process of defining the scientific endeavours.

Rationale for in vivo dosimetry in brachytherapy

As an attempt to define the rationale of in-vivo dosimetry in brachytherapy several issues are mentioned here. Some background considerations are additionally provided.

- *In vivo dosimetry is the only way to know what dose was actually delivered to the tumour and organs at risk, OARs. Brachytherapy procedures are performed without the safeguards of Record and Verify systems.*

Remote afterloading systems (RALs) are not equipped with verification systems similar to those used in linear accelerators. There is generally no measuring device on board to actually register if, where, and when the dose is deposited to the target volume. It must be mentioned, however, that some RAL systems have a connection to and can register readings from a diode detector type for bladder and rectal dose in GYN applications.

The only registration in the standard machines for HDR and PDR afterloading is the positional and temporal resolution of the source transfer through a catheter or applicator. However, this doesn't tell us anything about the position of the catheter or applicator in the patient.

- *Errors and dose miss-administrations in radiotherapy can result in:*
  - *underexposure of a tumour (geographic miss);*
  - *overexposure of OARs.*

Underexposure leads to a too low dose to the target volume and thus to a reduced chance of cure for the patient. Overexposure to known OARs or to tissues that are unintentionally irradiated due to geographic miss may lead to complications.

- *Human errors are the main cause of inadequate brachytherapy dose delivery, although mechanical failures occur as well. Examples are:*
  - *exchanged guide tubes;*
  - *misadjusted applicators;*
  - *reconstruction errors;*
  - *mechanical errors.*

The International Commission on Radiological Protection (ICRP) reports 86 (ICRP 2000) and 97 (ICRP 2005) as well as IAEA safety report series 17 (IAEA 2000) describe in detail many recorded

errors occurring in brachytherapy. From the analysis and the discussions in these publications brachytherapy errors and accidents are shown to be mainly related to human errors. Additionally, some errors are caused by mechanical events. Mechanical HDR events can be related to control units, computers, source cables, catheters, and applicators. Human errors relate to incorrect medical indication, patient identification, diagnosis or definition of the target volume, source strength, prescription, data entry, use of catheters or applicators. Some specific source positioning errors have been seen with the HDR afterloading techniques but different from LDR. Examples of such errors include applicator reconstruction errors, use of wrong applicator length or offset, wrong source step size, interchanged guide tubes, or afterloader malfunctions (IAEA 2000). Using a built-in dummy (i.e. non-active) check source, afterloader safety systems can detect certain dose-delivery errors (for example, mechanical obstruction of the source or improperly connected guide tubes). Some of these errors could have been detected by in vivo dosimetry, as for example a number of source positioning errors, which caused the radiation to be delivered outside the prescribed volume, resulting in under-dosage of the target. But, this also means that an unknown number of other brachytherapy errors remain undetected.

Results are highly dependent on physician skills

Brachytherapy is applied by a limited fraction of all radiation oncologists. It is often considered as a specialty, requiring a certain affinity with the manual clinical (almost: surgical) work. In several

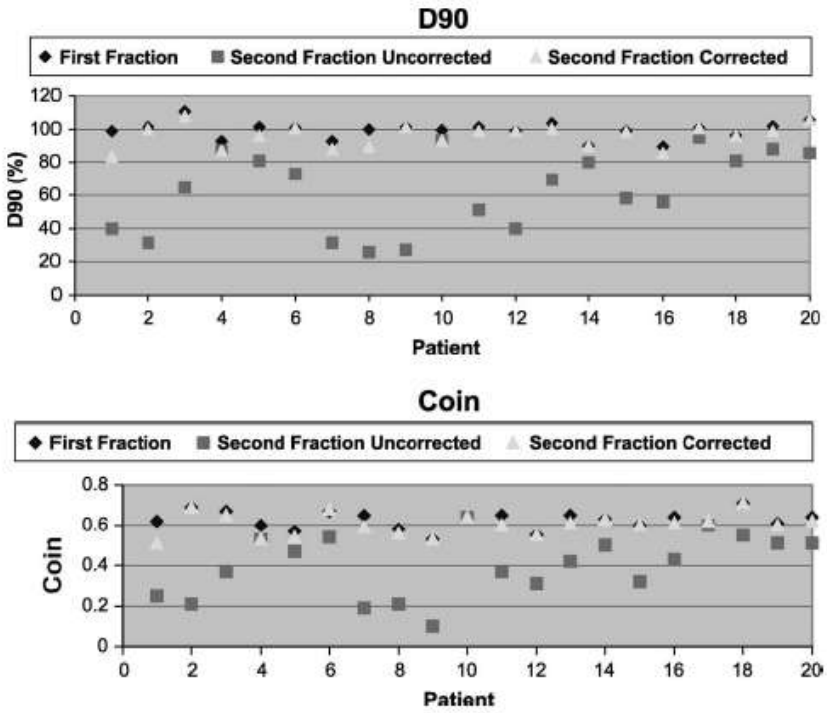

Figure 1 Individual patient values for D90 and COIN at first fraction, second fraction uncorrected and second fraction corrected as used for treatment.

publications it has been shown that a brachytherapy team often has a learning curve when applying new complex techniques, for example when introducing permanent prostate seed implants.

Movement of applicators

Only rarely the brachytherapy patients are irradiated in the same position as the applicators were inserted. Patients have to be moved from the operating theatre to an imaging department, after which

they are transferred to a ward before the treatment plan is ready and the irradiation can start. In between, and often more than once, transfer takes place from table to bed and to table again. One cannot reasonably assume an applicator to stay in exactly the same position. For example, Hoskin et al (2003) showed in a convincing way how much influence on quality parameters such as D_{90} and COIN index it has whether needle position in a 3-fraction HDR prostate implant technique is corrected for or not, guided by a CT-scan taken just prior to a new fraction (Fig 1).

- *Organ movement or deformation during treatment delivery:*
    - *LDR and PDR treatments are given over a prolonged treatment time, often with a duration of several days;*
    - *HDR implants are sometimes performed with a single insertion but with a low fractionation regime in the following 24 hours (e.g. 3 prostate HDR fractions);*
    - *permanent prostate implants clearly demonstrate the effects of organ swelling at the implant, after which the swelling slowly reduces in the next days and weeks.*

A treatment plan in these cases is usually based on the imaging of the application performed immediately after the implant. Bowel and bladder filling continuously changes the geometry over time, so the distance between applicators/source positions and the prescription point(s) changes with variations in dose as a consequence. In permanent LDR seed prostate implants, post implant dosimetry is recommended based on (CT) imaging 3-4 weeks after the implant, exactly for this reason of being representative for the full or effective treatment duration.

Brachytherapy includes a wide variety of techniques and applications. The rationale for using in vivo dosimetry in brachytherapy can be based on one or more of the considerations mentioned above. In a crude categorization one can define the possible roles of in vivo techniques in brachytherapy for:

- Commissioning of new treatment technique – " in vivo" in phantom;
- Quality control of patient treatments:
    - confirmation of delivered dose;
    - detection of errors;
- It can provide meaningful data for evaluation of treatment outcomes (TCP, NTCP);
- It can be used for intercomparisons and audit systems.

In vivo dosimetry at the same time is not able to solve all problems. One needs an experienced and well trained team of dedicated brachytherapy specialists (radiation oncologist, medical physicist, technologists and nurses) to be successful. Continuous education is a prerequisite to stay successful. High quality equipment must be available. Written protocols for both the physics quality assurance and for the clinical procedures must be present to describe the tasks and responsibilities (and where applicable the frequencies and tolerances) of the procedures for each member of the team. Specifically one needs to pay attention to the imaging procedures suited to the techniques used for the patient groups as shown in the typical example of Fig. 1.

Use of in vivo dosimetry is supported by (inter)national bodies. See for example for more details:

- ESTRO- the basic philosophy includes routine in vivo dosimetry as an important chain in Quality Control of radiotherapy including brachytherapy;
- IAEA – in a mission to improve the accuracy and safety of radiotherapy in developing countries;
- AAPM – TG-62 in a recommendation on the use of diode dosimetry in external beam radiotherapy (AAPM 2005).

Challenges for in vivo dosimetry in brachytherapy

Special challenges of in vivo dosimetry when applied to brachytherapy are related to the following aspects:

- *the high dose gradients;*
- *the short treatment distances – large effect of positioning errors;*
- *the low energy of the emitted photons from many brachytherapy sources;*
- *the uncertainties on source parameters;*
- *the shortcomings of dose calculation algorithms.*

High dose gradients are in the order of tens of per cent at short distances (5-20mm from the source). A typical dose prescription distance is 10mm. A one millimetre difference in distance corresponds with a change in dose rate of about 20% at that distance.

Compared to external beams, in many brachytherapy applications low energy emitting radioactive sources are used (e.g. ^{125}I, ^{103}Pd), in the energy range where the photo-electric interaction process dominates and detector response may vary over distance.

A thorough analysis of dosimetrical uncertainties was given in an AAPM report of task group 138 (DeWerd et al 2011), showing that there is about a 10% in the relative propagated uncertainty (at the k=2 uncertainty level) of the source dosimetry, comprising the calibration of the sources at the clinic, the determination of the TG-43 parameters and treatment planning interpolation steps for distances near the source.

Due to the approaches of the TG-43 formalism, used as a standard for dose calculation in brachytherapy, effects of tissue heterogeneity, non-water environment, ignoring lack of scatter conditions, ignoring shielding effects in an implant, deviations from the real dose can easily be in the order of >10% for common techniques as used in breast and prostate implants (Rivard et al 2009).

These considerations must be taken into account when choosing a detector system that is to be applied with an adequate accuracy of the measurement results that can be achieved.

Requirements of in vivo dosimetry in brachytherapy

For obvious reasons, in brachytherapy the detector system should have a certain robustness. As brachytherapy is for the greater part an invasive technique, detectors must be small and the application or positioning of the detector minimally invasive to the patient. The readout should be reliable, fast and preferably in real-time. The properties of the chosen detector will often only be a compromise of the following 'ideal' characteristics:

- *small size – high spatial resolution;*
- *high accuracy;*
- *high reproducibility;*
- *energy independent;*
- *response linear with dose over a broad range;*
- *dose rate independent;*
- *isotropic response - no directional dependence;*
- *safe;*
- *rugged and reliable (sterilization);*
- *comprehensive (both photons and electrons);*
- *real-time;*
- *efficient to use (fast set-up and reading);*
- *efficient to calibrate;*
- *affordable.*

Available detector systems

Detectors that have been developed and are commercially or non-commercially available to users comprise the following technology:

- *luminescence based detectors:*
  - *TLD*
  - *OSL*
- *diode;*
- *MOSFET;*
- *alanine;*
- *plastic scintillator.*

TLD materials

The most common thermoluminescent (TL) material used for dosimetry in radiotherapy is lithium fluoride (LiF). This material is usually doped with magnesium (Mg) and titanium (Ti), often denoted as LiF:Mg,Ti. It is commercially dependent on the per cent content of ^{6}Li and ^{7}Li isotope available in different forms such as TLD-100, TLD-600, TLD-700. Physical characteristics of TL dosimeters based on LiF and on other materials are described and discussed in detail by Kron (1999) including the advantages and disadvantages of these materials.

Compressed powder such as chips/rods (often called pellets) or ribbons in a Teflon matrix or loose powder are the most commonly used physical forms. Different processing is needed for each physical form and careful handling is a prerequisite in order to achieve acceptable reproducibility and, more importantly, good accuracy. Among others, Kron (1999) described the methods of calibrating and reading each type of TLD.

There are a few serious disadvantages of these dosimeters, one of which is the time it takes for using them in the entire process (calibration, preparation of the samples, annealing the samples, packaging and getting them ready for use, readout process). The waiting period between irradiation and readout to reduce the contribution of short lived peaks to the TLD output forms another drawback, while the fact that separate handling is needed makes them automatically suited only for off-line types of measurement. LiF TLDs can be used in a wide range of high energy beams in which they are almost energy independent (^{60}Co up to 25 MV x-rays). In contrast, in brachytherapy dosimetry the response of each TLD type must be characterized for linearity and energy dependence.

The solid form of the TLD is reusable and after each irradiation and readout of their response, they can be cleaned (known as annealing) and be ready for the next use, often with a next calibration cycle.

TLDs are in use for the dosimetry of linear accelerator beams including verification of machine output (photon and electron beams), for example in mailed audit systems as done by the Radiological Protection Center RPC at MDAnderson, Equal-ESTRO and IAEA. Other applications including patient treatment delivery verification in external beams and measurement of the dose received by pacemakers and implantable cardioverter defibrillators. TLDs are used for the dosimetry of LDR brachytherapy sources with low dose rates, but they have also proved useful for ^{192}Ir high dose rate brachytherapy source characterization, as demonstrated in numerous papers providing TG-43 data.

OSL and RL dosimetry

The principle of optically stimulated luminescence (OSL) dosimetry is very similar to that of thermoluminescence. When irradiated with ionising radiation, electrons or holes are trapped in crystal defects. The traps are stable at room temperature, making the crystal act as a passive dosimeter. Optical stimulation releases the electrons/holes to the conduction/valence bands and afterwards the

recombination energy is emitted as light. The luminescence signal is a measure for accumulated absorbed dose in the crystal. Furthermore, prompt recombination of holes and electrons during irradiation gives rise to immediate radioluminescence (RL). The RL signal depends on dose rate. In this way two different luminescence signals can be used for measuring both accumulated dose and dose rate, respectively.

A measurement system consists of an optical fibre system used to connect the crystal to a reader containing a stimulation source and detection system. The fibre carries both the stimulation signal to the crystal and luminescence signal from the crystal to the detector. The currently most commonly used OSL material is carbon doped aluminum oxide (Al_2O_3:C) due to its high sensitivity and negligible fading after irradiation.

The development and characterisation of OSL and RL dosimetry with Al_2O_3:C was initially performed with the purpose of clinical dosimetry in external beam therapy. Only later it was explored for use with ^{192}Ir sources. Commercial OSL systems have been developed, but the exploitation of the Al_2O_3:C RL signal in dosimetry is still far from a mature (plug-and-play) product.

The main advantage of Al_2O_3:C based dosimetry systems in brachytherapy is the high sensitivity, allowing to use small dosimeters. Furthermore, for both RL and OSL systems, stability and reproducibility has been found to be excellent (below 2.5% SD), with good temperature stability (better than -0.2-0.6% per ^{o}C) and limited angular dependence.

The effective atomic number of Al_2O_3:C is 11.3, resulting in an over-response for lower-energy photons (<300 keV). For brachytherapy, there is a considerable change of the energy spectrum with increasing distance from the source. This means that the water to crystal dose ratio increases with distance to the source. It is recommended to calibrate the dosimeters in the field of the brachytherapy source in clinical use.

Depending on the type of system, linearity with accumulated dose OSL has been shown up to ranges of 4 and 10 Gy, while supralinearity is present for higher doses. There is a dose rate dependence, but the sensitivity change is reproducible and therefore can be corrected and taken into account in a dosimetry protocol.

So far, the use of OSL and RL for in vivo dosimetry in brachytherapy is still limited with only one study reporting dose measurements in cervical cancer patients treated with PDR (Andersen et al 2009). In this study, in vivo dosimetry was performed in 5 cervical cancer patients who received pulsed dose rate (PDR) brachytherapy. The RL measurements were found to provide good visualization of the progression and stability of the brachytherapy dose delivery. It was concluded that RL dosimetry could have potential for on-line detection of brachytherapy errors in HDR and PDR treatments.

Diode detectors

Silicon diode dosimetry was analyzed in depth in the thesis by Rikner, of which the essentials for application in radiotherapy were described in the paper by Rikner and Grusell (1987). Diodes are widely used for the measurement of electron and photon beams. The following technical descriptions were taken from Cygler et al (2012). The relatively high silicon density results in a very high number of ionizations when the diode is exposed to radiation. There is no need for a large polarising voltage because the contact potentials within the diode are sufficient to prevent ion recombination. The sensitive part of the diode is the small junction between the p- and the n-type silicon. The p-type silicon is the silicon with boron or aluminium impurities, which absorb electrons from the surrounding silicon leaving positive (p) “holes” in the material. On the other side of the junction, the phosphorus impurities donate negative (n) electrons to the silicon. This imbalance of composition results in a

contact potential at the junction between the two dissimilar materials and a mopping up of the “free” ions, creating a few microns thick depletion layer. If the atoms in this depletion layer are ionized by radiation, then negative ions (electrons) will be attracted to the positively charged phosphorus impurities in the n-type silicon and the positive “holes” will diffuse towards the boron impurities in the p-type silicon. This flow of ions constitutes an ionisation current proportional to the incident dose.

Although all these detectors use both n-type and p-type material, some are described as p-type while others as n-type. The label identifies which material forms the larger part of the junction, being the p-type when the conduction is due to the movement of positive holes rather than electrons. Diodes can be operated with or without bias. In the photovoltaic mode (without bias), the generated current is proportional to the dose rate.

Dependence on dose, dose rate, energy, temperature and angle of incident radiation of the diode detector are generally well within acceptable limits. Diode based dosimetry systems are routinely used in some brachytherapy clinics, especially in treatments of gynecological cancers with rectal and bladder measurements using a direct reading. Currently, commercial systems are available from Isorad and PTW. A typical diode-based in vivo dosimetry system consists of an electrometer and different diode models.

MOSFET detectors

A MOSFET (Metal-Oxide-Semiconductor-Field-Effect-Transistors) detector is a semiconductor type of radiation detector. Principles of MOSFET operation and dosimetry have been described in much more detail elsewhere (see for a summary and further references: Cygler et al 2012).

Depending on its design, MOSFETs operate in active or passive mode during radiation exposure. In the active mode during the radiation exposure MOSFETs have a positive bias applied to the gate. This positive gate bias during irradiation reduces the recombination of electron-hole pairs and moves holes faster to the Si/SiO_2 interface. As a result the MOSFET has a higher sensitivity. For operation in passive mode, no bias is applied to the gate during the radiation exposure.

In principle, dosimetric properties of MOSFET detectors cannot be generalized. They strongly depend on the detector size and construction. As with all solid state dosimeters MOSFET sensitivity depends on radiation energy, increasing for lower energies. For photon energies lower than 200 keV, the sensitivity of the MOSFET detector increases considerably, by a factor of 3-6 reaching a maximum around 5-40 keV. This increase is dependent on the kind of detector. The detectors should be calibrated in the radiation field energy in which they are to be used. MicroMOSFETs have a practically isotropic response to radiation. Due to accumulation of dose, and dependent on the construction of the detector, MOSFETs have a finite life and need to be replaced regularly. This means costs for replacement and time for repeated calibration. Typically, MOSFET life is finished when the total threshold voltage reaches 10-20 V. More details can be found in a recent review (Cygler and Scalchi 2009). An example of the use of the detector system for urethral dose determination in permanent prostate implants is the work of E. Bloemen-van Gurp et al (2009a, 2009b).

EPR dosimetry

Electron paramagnetic resonance (EPR) or electron spin resonance (ESR) spectroscopy is a technique for studying chemical species that have one or more unpaired electrons like for example free radicals created during irradiation of some materials. In EPR dosimetry, the peak-to-peak amplitude of the first derivative EPR spectrum of radiation-induced radicals in the dosimeter is used to monitor the absorbed dose. Solid-state EPR spectroscopy has been used for dosimetry of ionizing radiation for many years (Regulla and Deffner 1982).

For EPR dosimetry in radiation therapy, L-α-alanine is the most commonly used material, although recently some new materials such as lithium formate have been tried. L-α-alanine is a non-essential amino-acid that occurs in the form of a white and odourless crystal powder. Other detector forms of alanine have the shape of rods, pellets, films etc. During irradiation of the amino acid L-α-alanine stable free radicals are produced, of which the concentration is proportional to the absorbed dose. This can be measured by Electron Paramagnetic Resonance (EPR) spectroscopy. Alanine, similarly to Fricke solutions belong to chemical type of dosimeters, since the determination of dose is based on a measurement of chemical changes induced by radiation.

Alanine as a dosimeter is relatively insensitive at low doses, which is the main drawback. Apart from the temporal stability of its signal, alanine as a detector of ionizing radiation has many attractive features. It has effective atomic number Z_{eff} (6.79) similar to that of water (7.42). Therefore the absorption of radiation energy by alanine is close to that in water. The energy response of this dosimeter is relatively flat above 150 keV. The absorbed dose coefficient is constant up to about 10 kGy. For doses above 6 Gy it's precision is comparable to that of TL dosimetry with LiF powder.

A useful feature of alanine is that it is independence of dose rate up to above 100 Gy/s (Regulla and Deffner 1982). Furthermore, alanine response is almost independent on temperature and humidity. Similarly to MOSFET and OSL dosimetry, the reading of the EPR signal is non-destructive which allows for permanent dose storage and multiple analyses of the irradiated samples.

In spite of all these attractive features, alanine has not been very commonly used in clinical practice. The main reasons are the relatively low sensitivity to low doses and to the rather complex ESR equipment needed to read the signals.

In brachytherapy, alanine has been used for source characterisation and for dosimetry in HDR applications. Some studies have been published on ^{137}Cs dosimetry and on beta dosimetry of ophthalmic applicators.

Plastic Scintillation Detectors (PSDs)

As further described by Cygler et al (2012), a plastic scintillation detector contains a light emitting scintillation component which produces photons proportional to the dose deposited in its sensitive volume. The light produced in the detector is optically coupled to an optical fiber guide and transmitted toward a photo detector.

The properties of plastic scintillation detectors have been studied for high-energy external beams (Beddar et al 1992a, 1992b). High spatial resolution, linearity to dose, independence of response for megavoltage energies, temperature independence and water equivalence are among the advantages that have been demonstrated for such detectors. Cerenkov light production has also been identified in the optical guide (Beddar et al 1992a, 2004). This light component is produced in the fiber when struck by radiation over a certain energy threshold, which depends on fiber material, and needs to be removed to perform accurate dosimetry. Using these detectors, possibility of real-time in vivo dosimetry has been demonstrated under external beam radiation and accuracy of better than 1% has been achieved.

Plastic scintillation detectors could be very useful to perform an accurate on-line in vivo dosimetry during ^{192}Ir HDR brachytherapy. Typical sizes of PSDs could be easily inserted in catheters used in this modality. Because the energy emission spectrum of an ^{192}Ir radiation source is mainly over the Cerenkov production threshold energy, the need for a removal technique has been stressed for clinically relevant situations. Lambert et al (2007) performed a comparative phantom study of PSDs to other commercially available detectors (MOSFET, diamond detector and TLD). Based on size,

accuracy and real-time possibilities, the authors claimed that PSDs showed the best combination of characteristics to perform dosimetry during ^{192}Ir HDR brachytherapy.

A study using an array of 16 PSDs in an insertable applicator that enables quality assurance of the treatment delivery and provides an alert to potential radiation accidents during HDR brachytherapy treatments has been performed by Cartwright et al (Cartwright et al 2010). The system presented is capable of measuring doses for 1 s exposures with an uncertainty between 2 and 3% for most of the PSDs. The extent to such an in vivo dosimetry system would be to allow the clinicians to carry out dose escalation to the tumour volume while avoiding rectal side effects.

Based on the results shown so far by the different groups involved in the field, the use of PSD is promising as a quality assurance approach when performing ^{192}Ir HDR brachytherapy treatments. However, to date, there have been no in vivo brachytherapy measurements performed in patients.

Short overview of characteristics of dosimeters

A summary of the main physical properties of the dosimetry systems discussed in the previous paragraphs is provided in the Table 1, copied from Cygler et al (2012).

Table 1 *Characteristics of various in vivo dosimetry detectors (from: Cygler et al 2012).*

Detector	cables	Bias voltage	Dose	Dose -rate	Energy dependence	Temperature dependence	Angular dependence
TLD	-	-	+	-	+	-	-
diode	+	+/-	+	+	+	+	+
MOSFETs	+/-	+/-	+	-	+	+/-	+/-
OSL/RL	+/-	-	+/-	+/-	+	+/-	+/-
PSD	+/-	-	+	+	+	-	-
EPR	-	-	+	-	-	+	-

"+" dependence present;

"-" no dependence present;

"+/-" dependence may be present, or somewhat, or for given detector types.

Other considerations for in vivo dosimetry in brachytherapy

The data of the previous sections and the characteristics shown in Table 1 can guide us in the decision what type of detector we should use for specific goals. But even then, other issues must be considered before it can be applied clinically. A number of these are listed in this section with a short comment.

The infrastructure of in vivo dosimetry.
Is the dosimeter positioned independently from the source applicators? Does it require a separate needle or catheter insertion or is it a non-invasive positioning? Who is responsible for each part of the measurement? Is it supported by the staff and all co-workers as it brings along additional work and it needs time?

Where to place the dosimeters and how to determine these positions?
Who places the dosimeter? Do we need a separate imaging step to determine its position? How long does it stay in place? Can it move? How is this secured? How do we make the relation with the data from treatment planning dose calculation?

What is the ability to detect treatment errors if they occur?
Is there an a-priori decision tree on the interpretation of the outcome of the measurement results? Do we simply register measured data and make an analysis of the procedure afterwards, or can we consider to interrupt the treatment when on-line data appear to indicate an error?

Probability of false alarms?
Is the system robust enough or do we have a considerable risk of having false alarms?

Do we need criteria for error classification?
Is each type of possible error equally serious or do we need to classify certain types of errors?

Do we need a QA-procedure for the vivo systems?
What are the requirements for quality assurance of the dosimetry system itself to ensure that methods and measurement results are stable and robust over prolonged time?

Such considerations make clear that, before an additional system can be introduced in a brachytherapy clinic, it needs to be well prepared. One will need to demonstrate that the in vivo dosimetry is feasible, that it serves the intended purpose and that it works in the clinic. Proper training of the team members for their respective roles is essential.

Other questions relate to the person of the patient undergoing the brachytherapy treatment, such as: does it mean an extra invasive step, extra time adding to the overall time of the procedure, should we explain what we are doing?

Maybe the most relevant question is, after analyzing all pros and cons of the proposed in vivo dosimetry step, its justification: what is the relevance of this specific vivo dosimetry? It is of utmost importance that the benefits will definitively outweigh the negative aspects.

Conclusions
There is a variety of systems and detectors available for use with brachytherapy. However:

- No single detector is perfect for all situations;
- The purpose of the in vivo step needs to be a priori well defined;
- The user has to understand the pros and cons of each system to select the best one for the task.

In general, much work has to be done for preparation and introduction of an in vivo dosimetry in the clinic. Staff has to be trained and fully supportive to the use of the system. Technically, much work needs to be done, e.g. for a careful calibration of the system, such as:

- Determination of energy dependence;
- Same with angular and eventually temperature dependence;

- Accurate localization of the dosimeter must be ensured.

Independently performed in vivo dosimetry in brachytherapy is the only way to verify what dose was actually delivered to the tumour and/or OARs. The output of the measurements can provide meaningful data for evaluation of treatment outcome. It can detect accidental over- and under-exposure resulting from undetected errors. In vivo dosimetry can be considered a useful tool whenever a new treatment technique is implemented.

In vivo dosimetry can be a burden for the brachytherapy department. In all cases, the proposed methods should be compared against other possible options that might serve the same goals, such as the use of extra imaging verification at each relevant step (planar X-ray, CT, even visual inspection of applicator movement). These latter methods are often able to identify serious faults in a system and can be undertaken with existing infrastructure.

Acknowledgements
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Patient-specific QA using 3D EPID dosimetry: future becomes reality

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Purpose/Objective

Dose delivery has become more complex nowadays with the use of Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). Patient-specific Quality Assurance (QA) with conventional dosimeters is time-consuming and often does not provide enough spatial information to accurately verify the delivered dose by a linear accelerator. Anatomical changes in a patient will also change the dose delivery to a patient and hence demand a patient-specific QA verification method to be performed in vivo. In this work, we will demonstrate that electronic portal imaging devices (EPIDs) are very accurate dosimeters that can be applied for both patient-specific 3D pre-treatment and in vivo dose measurements during clinical routine.

Materials/Methods

Portal images are acquired with indirect amorphous silicon (a-Si) EPIDs that are calibrated to absolute dose measured under full-scatter conditions. For this, a number of corrections are performed including a correction for backscatter, pixel sensitivity, off-axis EPID energy response differences and field size dependence. The dosimetric calibration model that is used can be applied to all commercial available indirect a-Si EPIDs. Incident energy fluence distributions per segment are calculated from portal dose images by applying several scatter corrections dependent on the verification procedure that is used (pre-treatment or in vivo dose verification). The fluence distributions are used to sample a phase space for a forward Monte Carlo (MC) simulation to obtain the 3D dose delivered inside a patient. For this work, 3D dose reconstructions are done based on the planning CT scans of phantoms and patients. This way, a direct comparison is possible between the 3D delivered dose and the 3D dose of the treatment planning system (TPS). The dose comparisons are performed using a 3D gamma evaluation method and a dose-volume histogram (DVH) analysis. The entire clinical workflow from image acquisition to analysis is automized by using a central Picture Archiving and Communication System (PACS) in combination with a number of parallelized DICOM services. Documentation of all dose verification procedures is done by PDF reporting.

Results

Different strategies are presented to reconstruct the 3D delivered dose to a patient. Two examples are presented here in figures 1 and 2. It will be shown that the EPID-based procedures are very accurate and allow for the verification of the dose engine of the TPS, treatment parameter transfer and the detection of patient-related dose delivery errors (e.g. patient setup and anatomy variations). All

methods are perfectly integrated in the clinical workflow within our department supporting the analysis of up to 10 TB of EPID dosimetry images yearly.

Conclusions

High-precision patient-specific QA using 3D EPID dosimetry is reality and can be applied large-scale during clinical routine. For full in vivo dosimetry resulting in a 3D delivered dose-of-the-day, Cone Beam CT scans can be used without drastically changing the calculation models and the clinical workflow as presented in this work.

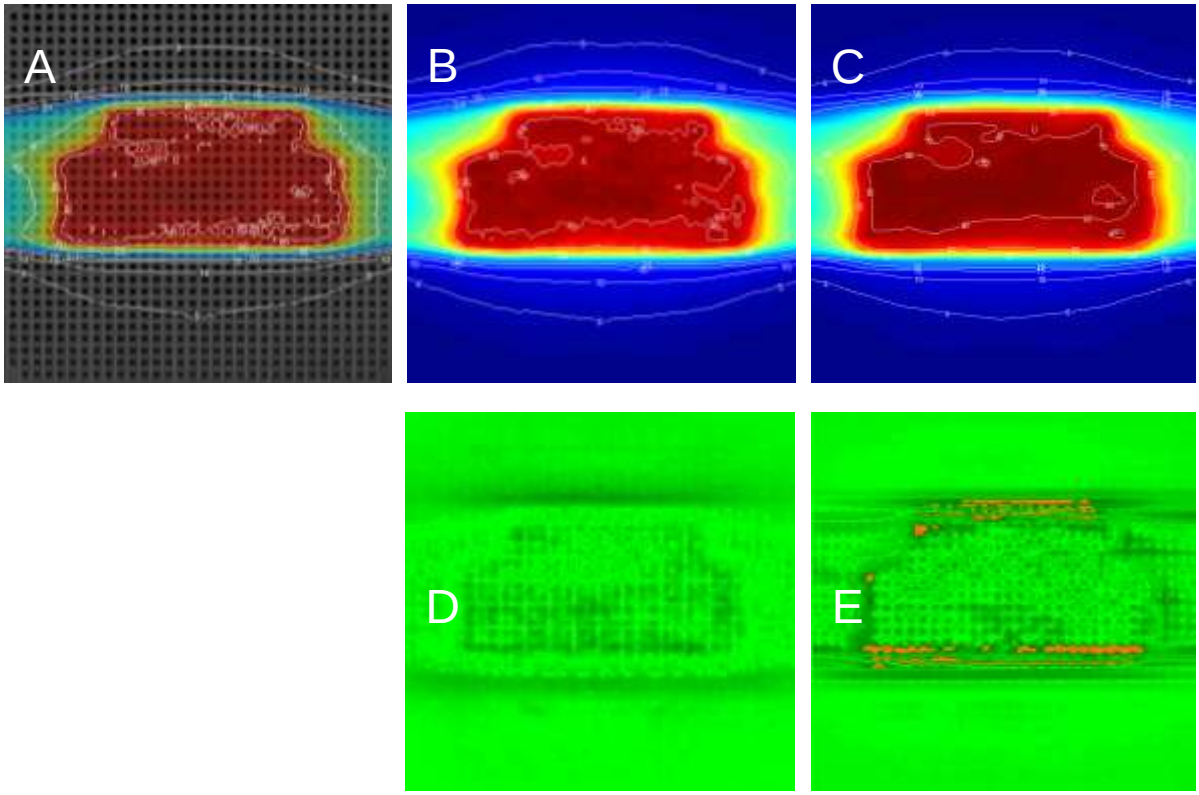

Figure 1: Pre-treatment EPID dose measurements are performed during the delivery of a VMAT technique and the 3D dose is reconstructed inside the CT scan of a MultiCube phantom embedding a MatriXX 2D ionization chamber array (both IBA Dosimetry, Germany). The reconstructed dose plane through the MatriXX detector array (B) is compared to a dose plane from the treatment planning system (Eclipse, Varian Medical Systems, Palo Alto, CA, USA) (A) by using a 3D gamma evaluation with global gamma criteria of 3% and 3 mm (D). The same comparison is performed between a measured dose plane using the MatriXX array (C) and the dose plane from the TPS (A), resulting in the gamma distribution shown in (E). No pixels with gamma values larger than 1 occurred in (D) while the percentage of pixels with gamma values larger than 1 in (E) was 2.1, 4.8, 4.3 and 3.9% for isodose level cut-off values of 0, 20, 50 and 80%, respectively.

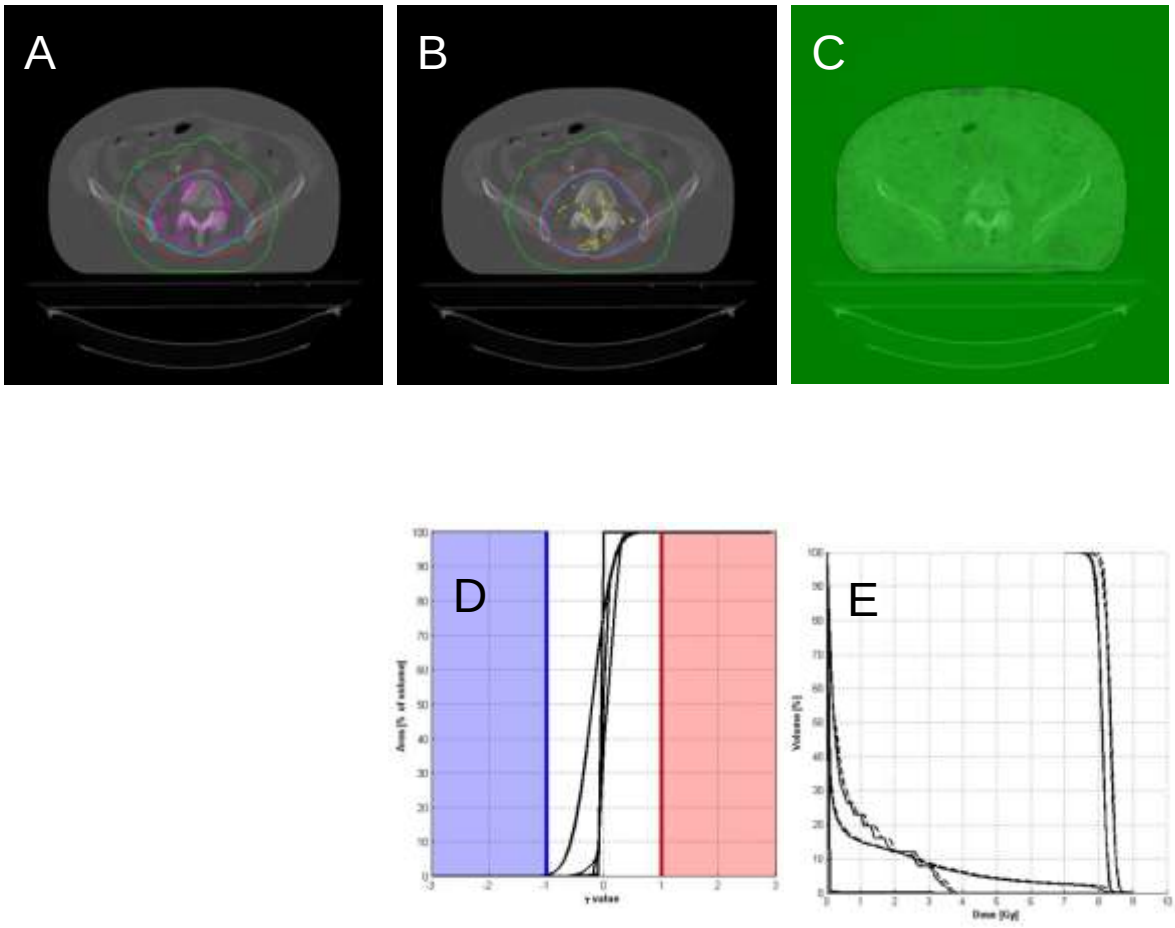

Figure 2: (A) 3D dose distribution from the TPS (Eclipse, Varian Medical Systems, Palo Alto, CA, USA) for the same VMAT treatment technique as applied in figure 1. (B) 3D reconstructed dose distribution based on pre-treatment EPID dose measurements and reconstructed in the planning CT scan. (C) Comparison of the two 3D dose distributions in (A) and (B) by using a 3D gamma evaluation with global gamma criteria of 3% and 3 mm. (D) Cumulative gamma histograms and (E) cumulative dose-volume histograms for different volumes delineated in the TPS.

In-vivo dose verification for particle therapy

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Introduction

The major issue in any form of radiotherapy is that the tumor dose is restricted by the dose delivered to the surrounding healthy tissues, which must be kept low enough to avoid complications. Therapeutic particle beams (mostly consisting of protons or carbon ions) have physical advantages over conventional photon beams, as most of the dose is deposited in a narrow region at the end of the particle range (the Bragg peak). Nevertheless, turning the physical advantages of particles into true clinical benefits requires that the Bragg peak be aimed at the tumor with millimeter accuracy.

In practice, errors occur due to range uncertainties (e.g. due to due to the conversion of CT data into ion interaction data), positioning errors, organ motion, and anatomical changes during the course of treatment. This makes it necessary to verify the delivered dose distribution in-vivo during the treatment. The goal of such treatment verification is the unambiguous detection and measurement of a deviation in treatment delivery from the treatment plan.

Because the particle beam is stopped within the patient, portal imaging devices [1] cannot be inherited from photon therapy. Instead, verification must rely on secondary radiation correlated to the in-vivo dose and detected during or immediately after treatment. Such secondary radiation results from the small fraction of particles that undergo nuclear interactions with nuclei in the body during irradiation. Two types of secondary radiation have been considered for treatment verification, see figure 1. The first consists of 511-keV annihilation photon pairs, which follow the decay of the small amount of β+-emitters created by the nuclear reactions and typically occur on a timescale of minutes to tens of minutes [2-5]. The second type consists of “prompt” gamma radiation [6-7] emitted from excited nuclear states on a pico- or femtosecond timescale following the nuclear interactions.

Motivated by the imminent introduction of proton therapy in The Netherlands, several Dutch groups are investigating a number of approaches to utilize these secondary radiations for particle therapy treatment verification.

In-situ PET

At present, the only means of non-invasive proton dose verification that has been tested clinically is based on the coincident detection of annihilation photon pairs to reconstruct a three-dimensional image of the β+ activity created by the therapeutic particles, i.e. positron emission tomography (PET). Although convincing proof-of-principle data has been acquired in several clinical trials, these initial tests still had many shortcomings.

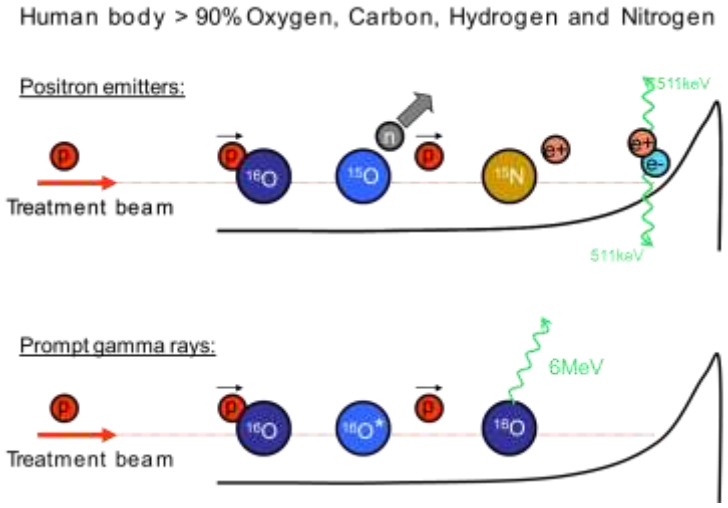

Figure 1. The highly energetic protons (p) used in radiation therapy not only deposit dose (black curves), but a small fraction of them also undergo nuclear reactions, producing □+ emitters (top) and prompt gamma radiation (bottom). Figure by D.C. Oxley for the ISoToPE project, a TU Delft - KVI/RUG collaboration funded by FOM project 09NIG18.

For example, the method relies on Monte Carlo simulations to predict the β+ emitter distribution from the treatment plan, which is then compared to the measured distribution (Figure 2). These simulations are quite complex and rely on cross sections to transform the particle fluences into activity distributions. Different Monte Carlo codes employ cross sections from different experimental databases or theoretical models. They may also differ in the physics transport models of the primary particles and their secondaries. This may cause inherent uncertainties for dose verification. A consortium of researchers from the MAASTRO clinic, Delft University of Technology (TU Delft), and several German, French and Belgian groups recently published an extensive investigation of these uncertainties [8]. This study clearly points to the need to provide more reliable data in Monte Carlo codes: mostly cross sections, but to a lesser extent also transport models and even ionization potentials.

Other important shortcomings in the early trials were related to the PET imaging instrumentation used.

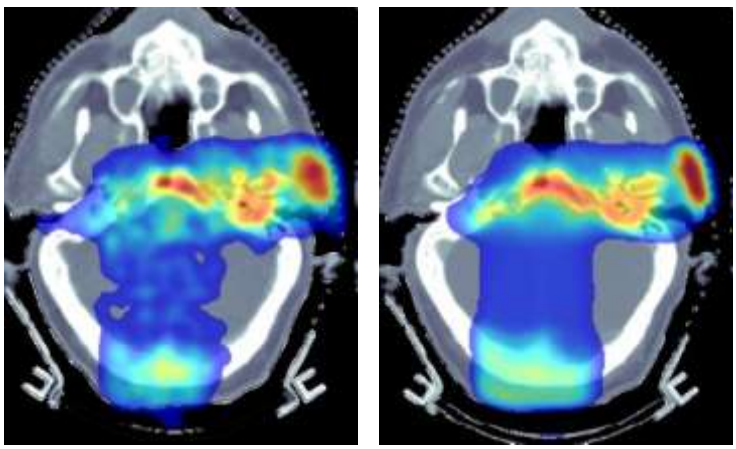

Figure 2. Activity distribution after two-beam proton irradiation at Massachusetts General Hospital. Right: predicted with Monte Carlo. Left: measured with PET scanner outside treatment room. Images by K. Parodi, Ludwig Maximilians University (LMU) and Heidelberg Ion-Beam Therapy Center (HIT).

In some studies, the patient was brought to a conventional PET scanner directly after the irradiation. These studies were affected by positioning errors as well as radioactive decay and biological washout of the positron emitters [9-11]. The amount of β+ activity generated in particle therapy typically is an order of magnitude lower than in a standard clinical PET scan, and therefore the use of an *in-situ* PET device, integrated in the treatment delivery facility, has the important advantage that it minimizes the loss of the short-lived β+ emitters. However, this approach is technically more challenging and studies with early prototypes of such devices have indicated that a number of improvements are necessary [11-13].

For example, increasing system sensitivity is of primary importance. This requires maximization of the detection efficiency of the detectors and the solid-angle coverage of the scanner. The latter is especially challenging for in-situ PET as the PET system must not get in the way of the proton beam. Therefore, extremely compact detectors are required that allow unconventional scanner geometries, see e.g. figure 3. The detectors also need to be radiation-hard and magnetic-field compatible as the PET system is located close to the last bending magnet of the treatment gantry.

A major breakthrough could be accomplished by using time-of-flight (TOF) PET. In TOF-PET, the difference in the arrival times of the gamma quanta is used to roughly localize the position of annihilation along the line-of-response (LOR), see figure 4 (left). During image reconstruction, see figure 4 (right), the TOF information is used to "confine" the event to the most probable section of the LOR. The width Δx of this section depends directly on the coincidence resolving time (CRT) Δt: $\Delta x = c \bullet \Delta t / 2$. As a result, image quality and dose quantification improve dramatically and, furthermore, limited-angle artifacts can be eliminated, provided that a CRT < 200 ps (Δx < 3 cm) can be realized [14].

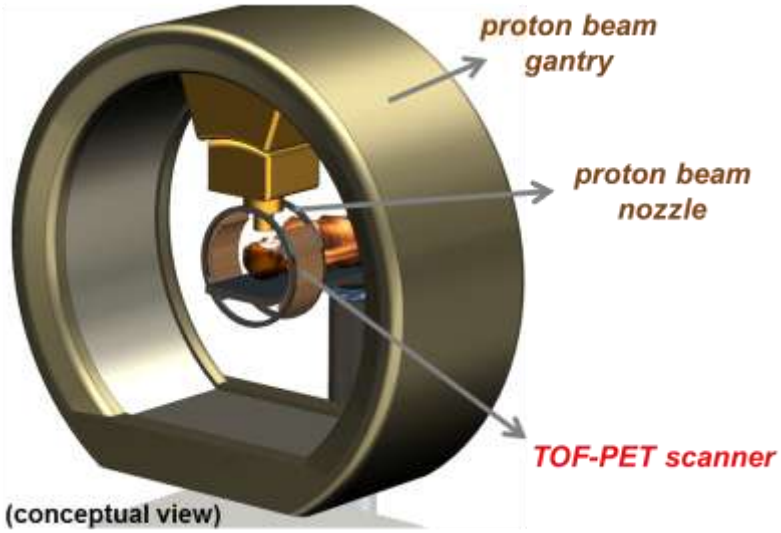

Figure 3. Schematic representation of a dual-panel (or partial-angle), in-situ TOF-PET device integrated in a particle therapy treatment gantry. Figure by KVI/RUG for the ISoToPE project, a TU Delft - KVI/RUG collaboration funded by NIG-FOM project 09NIG18.

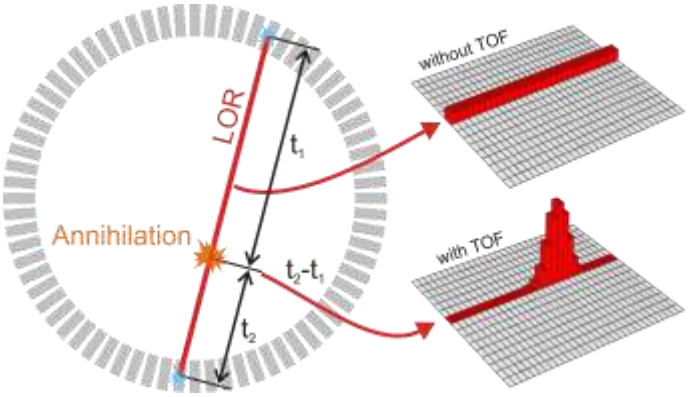

Figure 4. Time-of-flight PET. The difference in arrival times t2 – t1 is used to localize the event along the line-of-response (LOR).

TU Delft and the Kernfysisch Versneller Instituut of the University of Groningen (KVI/RUG) aim to make use of their expertise in the development of novel, compact, magnetic-field-compatible TOF-PET detectors, currently under development for application in clinical PET and PET-MRI scanners [15-17], to realize the first clinically useful time-of-flight in-situ PET device.

Prompt gamma imaging

Prompt gamma radiation may in principle allow for real-time, in-situ monitoring of the treatment delivery, in particular the particle range within the patient, by imaging the emitted prompt gamma rays. Prompt gamma imaging can be achieved in different ways. For example, a single, collimated detector can be moved parallel to the beam axis to measure the profile of perpendicularly emitted prompt gamma photons [6,18-19]. To enhance detection efficiency, one may use a planar or confocal multi-slit collimator [20]. In these approaches the function of the collimators is to reject photons that are emitted from the patient in directions other than perpendicular to the beam axis. In another approach, a knife-edge slit collimator is used to project an image of the prompt gamma emission onto a gamma camera [21-26]. Collimator-free imaging of the prompt gamma emission is being investigated using several different Compton camera designs, i.e. multi-stage measurement devices capable of determining the initial energy and direction of a gamma photon as it undergoes Compton scattering within the different stages of the detectors [29-34].

The detection of (highly energetic) prompt gamma radiation is technologically challenging, and no clinical studies have been performed to date. Monte Carlo study on the use of prompt gamma emission as a method to verify the accuracy and efficacy of doses delivered with proton radiotherapy nevertheless indicate that a strong spatial correlation should exists between the delivered spread-out Bragg peak (SOBP) and the characteristic prompt gamma production [7]. Figure 5 provides an example of a potential prompt gamma imaging device based on slit collimation.

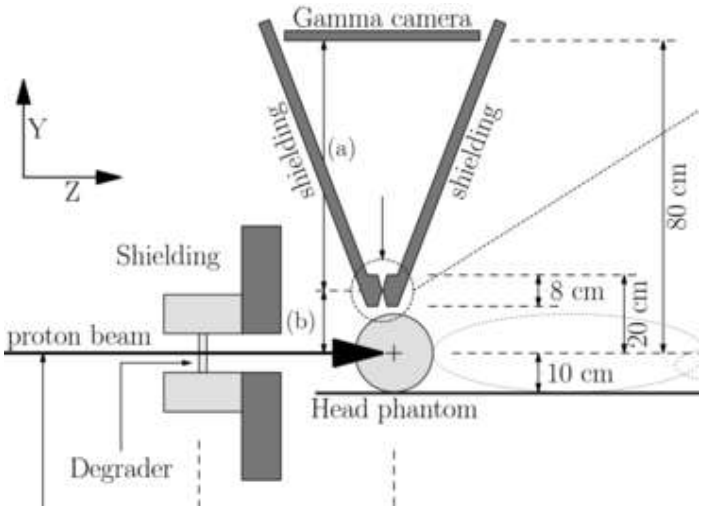

Figure 5. Proposed slit camera for real-time Bragg peak position verification in particle therapy. Image taken from [28].

In all prompt gamma based approaches, a considerable background signal resulting from the simultaneously created neutrons may obscure the prompt gamma image. This background signal may result from direct interactions of the neutrons in the detectors and/or from gamma photons produced by the neutrons within the collimators and/or other structures surrounding the detectors. As the neutrons are strongly scattered within the body of the patient, their spatial and directional correlation with the dose profile is lost and their effect on the prompt gamma image can only be detrimental.

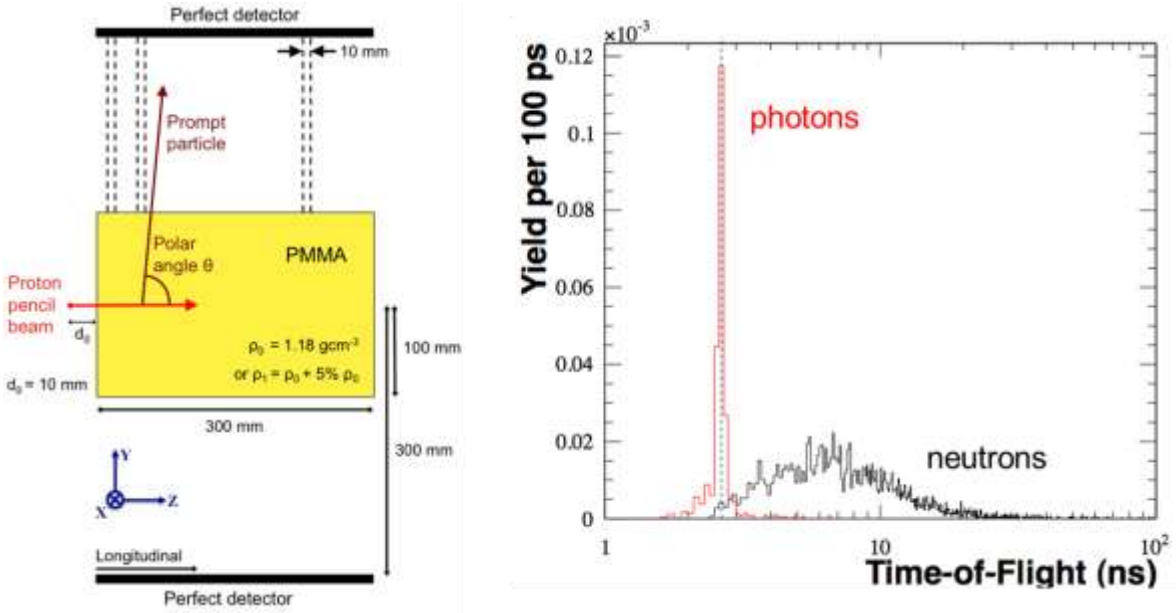

Figure 6. Longitudinal cross-section (left) of the simulation setup. The incident protons are assumed to be mono-energetic and the beam shape is pencil-like. The cylindrical PMMA phantom, placed in air, has a diameter of 20 cm and a length of 30 cm. The inner diameter of the detector is 60 cm, while its length is equal to that of the PMMA phantom. The graph (right) shows the TOF spectra of the prompt gamma photons (grey) and neutrons (black) impinging perpendicularly on the 10 mm wide detector region indicated in the left-hand figure. Images taken from [35].

Inspired by the work of Testa *et al* [18], TU Delft is investigating a method for neutron background rejection based on a shifting time-of-flight (TOF) acceptance window to enhance the accuracy of prompt-gamma-based range verification in pencil beam scanning proton radiotherapy [35]. This method utilizes the fact that neutrons travel slower than gamma photons and in principle is compatible with any of the previously outlined prompt gamma imaging approaches. Figure 6 shows some results of a Monte Carlo simulation of this method.

The application of a shifting time-of-flight window that accounts for the propagation of the protons through the patient appears to reduce the neutron background by a large factor, even if the non-idealities in the time structure of cyclotron-produced therapeutic proton beams are taken into account. Work is underway to demonstrate this method with proof-of-principle experiments in therapeutic beams.

Conclusion

Treatment verification through the imaging of annihilation and/or prompt gamma radiation emitted from the patient upon treatment delivery is crucial to further improve particle therapy. The wide experience with image-guided radiotherapy (IGRT) techniques in Dutch medical centers, in combination with the active research on novel gamma radiation detection technologies for nuclear medicine applications such as SPECT, TOF-PET and PET/MRI, puts The Netherlands in an excellent position to play a leading role in the development of clinically useful particle therapy treatment verification instrumentation and methodology.

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High and low dose regions to normal tissues in IMRT

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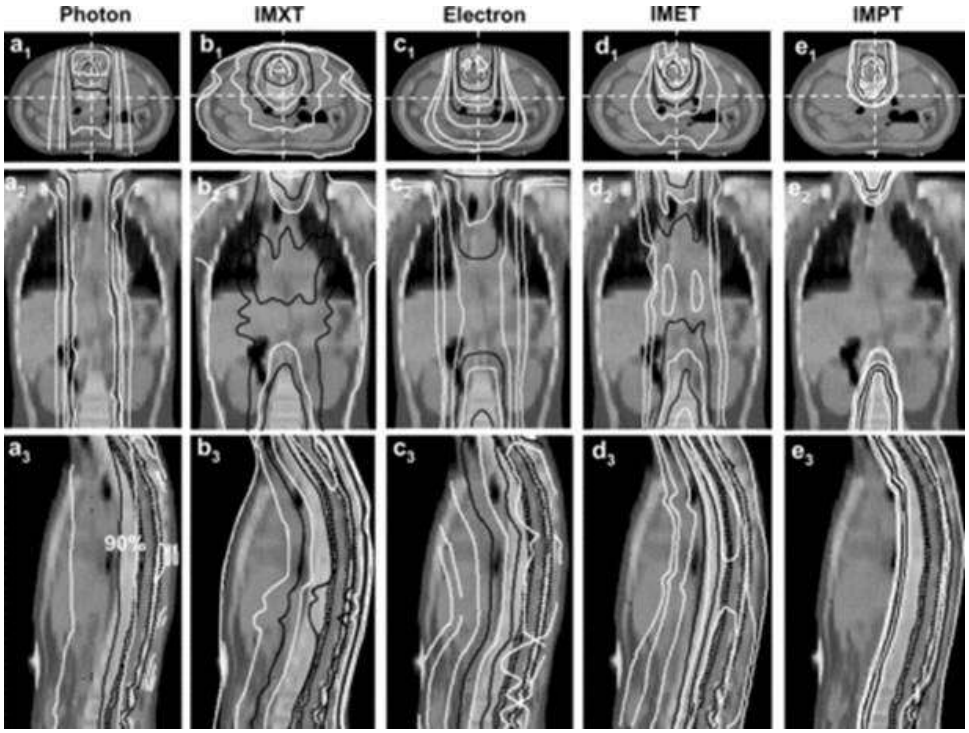
IMRT is focused at side effects in order to increase the target dose and to decrease the normal tissue dose. This involves multiple directions of radiation and potentially more low dose volumes. IMRT is, generally, not aiming at reducing secondary cancers. In regions with dose limiting organs at risk (OAR's) nearby, IMRT enables the delivery of a higher dose and thereby increased local control (as shown in lung- and prostate cancer). IMRT decreases side effects and/or increases coverage when dose is kept equal.

The delivery of radiation doses by means of IMRT leads to an increased number of monitor units and thereby a larger total-body radiation dose. The absence of wedges somewhat compensates for the increased head-scatter dose. In short; IMRT leads to a larger volume of normal tissue exposed to lower radiation. The consequences of these effects will relate to dose-response curves for radiation induced carcinogenesis. For adult patient, the benefit/cost balance for radiation is most likely in favor of IMRT for all cases since the potentially induced secondary malignancies in general exceeds life expectancy. For children, on the other hand, life expectancy is much larger due to the success of modern cancer treatment.

Low radiation doses to normal tissues are especially clinically relevant in pediatric radiotherapy. The estimated risk of secondary lethal cancers after IMRT are probably 1.5 times higher than after conventional photon beam arrangements, but may be 6 times less prevalent after intensity modulated proton beam radiotherapy (IMPT). The incidence of late secondary neoplasias are dependent upon total dose applied, the age at which the patient was irradiated and the tissues involved. The value of IMPT in its potential to reduce late secondary neoplasias is intuitive and hypothetical and needs to be proven in large prospective clinical trials.



Late effects after radiotherapy in childhood cancer survivors

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Abstract not published

Cell survival following high dose rate flattening filter free and conventional dose rate irradiation

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Introduction

Intensity Modulated Radiation Therapy (IMRT) has become one of the standard irradiation techniques in most institutes. By modulating the radiation beam using a multi-leaf collimator (MLC) using stationary beams or as a Volumetric Modulated Arc Therapy (VMAT) [1], conformal dose distributions to the target volume can be obtained while minimizing the dose to adjacent critical normal tissues. VMAT allows high conformal three-dimensional dose distributions to be delivered in one or two gantry arc rotations. During this rotation, there is continous variation in the shape of the aperture, rotation speed and dose rate

To homogenize the beam, the linear accelerator contains a flattening filter. Since in IMRT inhomogeneous beams are used, there is no need for a flattening filter. Flattening filter free (FFF) beams can deliver higher dose rates and therewith potentially shorten the delivery times. Faster irradiation is of particular benefit in stereotactic body radiotherapy (SBRT) where high fraction doses are delivered with long beam-on-times [2,3]. The omission of the flattening filter creates a beam with a non-homogeneous fluence distribution. Resulting dose rates can be as high as 2.400 MU/min, resulting in a maximum dose rate of 24 Gy/min. In addition to the higher average dose rate, the dose per pulse is also increased by a factor of 4 [4], leading to instantaneous dose rates exceeding 10^4 Gy/min.

With VMAT compared to IMRT, a larger normal tissue volume is exposed to a lower irradiation dose. Furthermore, the dose rate in VMAT FFF is 3 to 4 times higher than with FF irradiation. The implementation of these novel irradiation methods in the clinical practice prompted the discussion about its clinical / radiobiological consequences. There is concern regarding late normal tissue side effects, second cancer risk as well as therapeutic efficacy on normal tissue and tumour cells, which is the focus of the present paper.

The effect of high dose rate FFF beams and standard dose rate flattened beams was investigated on three human cancer cell lines. Clonogenic cell survival was determined following single dose irradiation and the number of surviving clonogenic cells was estimated in a fractionated irradiation protocol with five daily fractions.

Materials and methods

The human astrocytoma cell line D384, the glioma cell line T98 and the human lung carcinoma cell line SW1573 were irradiated using either a single fraction (0- 12 Gy) or multiple fractions of 2 Gy (D384 cells) or 3 Gy (SW1573 cells). Cells were irradiated inside a phantom using standard fixed gantry beams with a sliding window technique to create homogeneous dose distributions over the surface of the cell cultures. FF beams were delivered at their maximum dose rate of 600 MU/min, with 360 pulses per second and pulse width of 4.5 µs. FFF beams were delivered at their maximum dose rate of 2400 MU/min, with 360 pulses per second and pulse width of 4.5 µs. In the experiment and the dose calculation, the surface source distance was chosen at 86 cm to ensure that cells received a

dose rate between 21 and 29 Gy/min (mean of 24 Gy/min and average dose rate per pulse 1.5 10^4 Gy/min). The plans for the flattened beams also used an inversely optimized sliding window, in order to provide a similar treatment technique as for FFF beams. Flasks were positioned at a surface source distance of 95 cm, delivering a dose rate between 5.6 and 5.9 Gy/min (mean of 5.86 Gy/min and average dose rate per pulse of 3.6 10^3 Gy/min). Following treatment, cell survival was determined by clonogenic assay. In the fractionated irradiation set-up, the number of clonogenic cells was estimated by including tumour cell proliferation during the 4 days overall treatment time in the analysis [e.g. 5].

Results

Using the sliding window technique for irradiation of cells, the total delivery time was higher than for open beams. For example, delivery of a fraction of 4 Gy lasted 58 seconds for the FF beam and 28 seconds for the FFF beam.

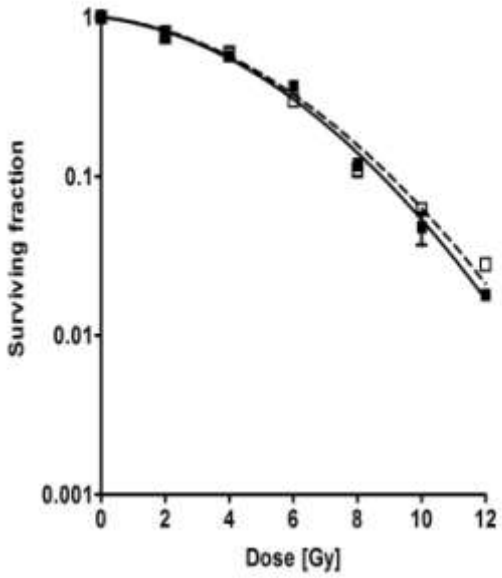

Figure 1. Clonogenic survival of SW1573 lung carcinoma cells after FF (open squares) and FFF (close squares) irradiation. Error bars represent the standard error of the mean (n=4).

Figure 1 shows cell survival of SW1573 lung cancer cells following single fraction irradiation not to be significantly different between FF and FFF irradiation. Similar data were obtained for the T98 glioma and D384 astrocytoma cell lines. Irradiation of SW1573 cells with five fractions of 3 Gy, reduced cell survival to ~ 3%. The number of clonogenic cells after the irradiation course amounted 26450 $\pm$ 669 (FF) and 25206 $\pm$ 1084 (FFF) (n.s.). Fractionation results on D384 glioma cells were basically the same.

Discussion

The present data show that an approximate 4 fold increase in instantaneous dose rate, increasing the average dose rate from 6 Gy/min to 24 Gy/min by changing from an FF to an FFF beam, results in equal biological effects, both on the endpoints ‘clonogenic cell survival’ and ‘number of clonogenic cells’. This was observed for three human cancer cell lines after single fraction irradiation. To better mimic the clinical situation, we also performed fractionated irradiation for two cell lines, with similar results.

With traditional external beam irradiation techniques, clinical irradiation is typically applied at maximum dose rates in the order of 5 Gy/min which is now increased with FFF technology to over 20 Gy/min.

Experimental data on the effects of high mean dose rates – and ultra high average dose rates in the pulse – are however scarce. Lohse et al. [6] described equal survival of T98 and U87 glioma cells after FF and FFF irradiation up to a single dose of 5 Gy, but they observed a slightly lower cell survival for cells irradiated with an FFF beam at 8 Gy and higher. Our data are consistent with those of Sorensen et al. [7] who also reported no dependence of cell survival on the instantaneous dose rate. Their experiments were performed on two cell lines that were irradiated with single doses up to 10 Gy. However, instead of a real FFF beam, they used a regular flattened beam where the distance of the cells to the accelerator was varied, thus enhancing the dose rate up to 29.9 Gy/min, and comparing to dose rates of 5 Gy/min. Lohse et al. [6] compared the effect of dose rates varying between 0.2 and 24 Gy/min and they concluded that only high instantaneous dose rate resulted in decreased cell survival, even if delivered with lower average dose rate. In the present study, irradiation using high instantaneous dose rate and high average dose rate (average 24 Gy/min) was compared with irradiation using lower instantaneous and average dose rate (5.86 Gy.min). Furthermore, different from the experimental procedure used by Lohse et al. and Sorensen et al. [6,7], we used a sliding window to deliver a homogeneous dose from the conical FFF dose profile. For consistency, a similar sliding window, although with a slightly larger window width, was created for flattened beam irradiation.

Radiobiological experiments are restricted so far to in vitro studies only. Of concern could be a possible higher radiobiological effect of FFF beams on normal tissues and healthy organs. FFF beams are nowadays used at maximum dose rate of 2400 MU/min for lung and liver SBRT treated with RapidArc (Varian Medical Systems) at fraction doses above 11 Gy [8]. Lower fraction sizes are obtained by removal of pulses from the beam, resulting in a lower average dose rate, but not by lowering the dose per pulse. Clinical experience so far has not shown any increased toxicity when using FFF beams.

Conclusion

Data from our laboratory together with literature data indicate equal biological effects regarding cell survival of FFF irradiation with a dose rate of 2400 MU/min and four times higher dose per pulse compared to irradiation with FF beams. Verification in an in vivo tumour / normal tissue model is required, together with long-term follow-up data from irradiated patients to finally conclude whether or not the biological effects of FFF irradiation equalize those after FF irradiation.

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Cataract risk at low radiation dose: seeing is believing!

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Abstract not published

The quantity H_p (3): need for reanimation?

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The International Commission on Radiation Units and Measurements, ICRU, has defined the so-called operational quantities for dosimetry in radiation protection. The most wide-spread quantity used is the one defined for individual monitoring: the personal dose equivalent, $H_p(d)$ (ICRU, 1992). The personal dose equivalent is the dose equivalent in soft tissue below a specified point on the body, with parameter *d* identifying the "appropriate depth" in mm. The question which depth is to be regarded as appropriate originally was answered by the characterization of the radiation field, as either weakly of strongly penetrating. The current practice is that the depth should be appropriate to estimate a given limiting quantity, either effective dose, E, or equivalent tissue dose, H_T, for a given tissue. Personal dose equivalent at 10 mm depth, H_p (10), is commonly considered to be a good estimate for effective dose, and personal dose equivalent at 0.07 mm, H_p (0.07) is regarded as a good estimate for equivalent skin dose. Furthermore, 3 mm depth was recommended as the appropriate depth for measurement of the equivalent eyes lens dose, H_{lens}.

The past two decades, the quantities $H_p(10)$ and $H_p(0.07)$ have grown to maturity: a complete metrological infrastructure was developed, with the exception of primary standards. Traceability in absence of primary standards for the operational quantities was solved by the development of written standards by ISO/IEC, harmonizing the use of reference radiation qualities, calibration phantoms and conversion coefficients, converting air kerma to the operational quantities. A wide range of commercially available dosemeters, type tested to both the quantities $H_p(10)$ and $H_p(0.07)$, nowadays has become available from equipment suppliers and approved dosimetry services.

Unlike its well-developed sister-quantities $H_p(10)$ and $H_p(0.07)$, the quantity $H_p(3)$ lacked popularity from the start. With its introduction, ICRU already stated that "monitoring of $H_p(3)$ will be required only in unusual circumstances", because it was assumed that the limit for the equivalent eye lens dose (150 mSv per year) would not be exceeded when the limits for the effective dose (20 mSv per year) and for the equivalent skin dose (500 mSv per year) are not exceeded. Discussions about what would be an appropriate calibration phantom ended non-conclusive, and consequently no consensus was reached on which values for conversion factors should be used. In its 2007 recommendations (ICRP, 2007) ICRP concluded that, since the quantity $H_p(3)$ seemed to have been be abandoned by the complete radiation protection community, with virtually no dedicated instruments available to measure it, it might be better to end its cumbersome life.

Surprisingly, in the same 2007 Recommendations, the ICRP recognized "that further information is needed and revised judgments may be required particularly in respect of the eye". Recently ICRP issued a "Statement on Tissue Reactions" (ICRP 2011) including a recommendation to reduce the annual limit for equivalent dose to the eye lens from 150 mSv to 20 mSv (a factor of 7.5!). Implementation of this recommendation into national legislation is only a matter of time.

Of course, all this placed the future of the quantity $H_p(3)$ in a complete new light. Suddenly the need for monitoring dose to the eye lens was subject of debate again, and connected to this discussions questions around the metrology of the quantity $H_p(3)$ gains importance. Many initiatives have started,

with the ORAMED project probably contributing the most to the developments (Vanhavere et al, 2012), providing favorable conditions for a revival of $H_p(3)$.

Responding to questions about the eye lens dosimetry from the medical field, NRG started a program to explore the needs and possibilities for a new life of $H_p(3)$. As a first step, the suitability of the NRG standard whole body photon dosemeter for measuring H_p (3) was tested. Already available measurement data from type tests performed on the ISO slab phantom were re-evaluated, using $H_p(3)$ conversion coefficients calculated for the radiation qualities used in the type test. As expected, the detector at the so-called "B-position" in the NRG dosemeter (LiF TLD covered with approximately 0.4 g.cm^{-2} plastic filter) showed a response suitable to estimate H_p (3) (figure 1). With respect to energy response and isotropy, the response of this detector complies with the requirements for an eye lens dosemeter according to the ISO-12794 standard (ISO, 2000).

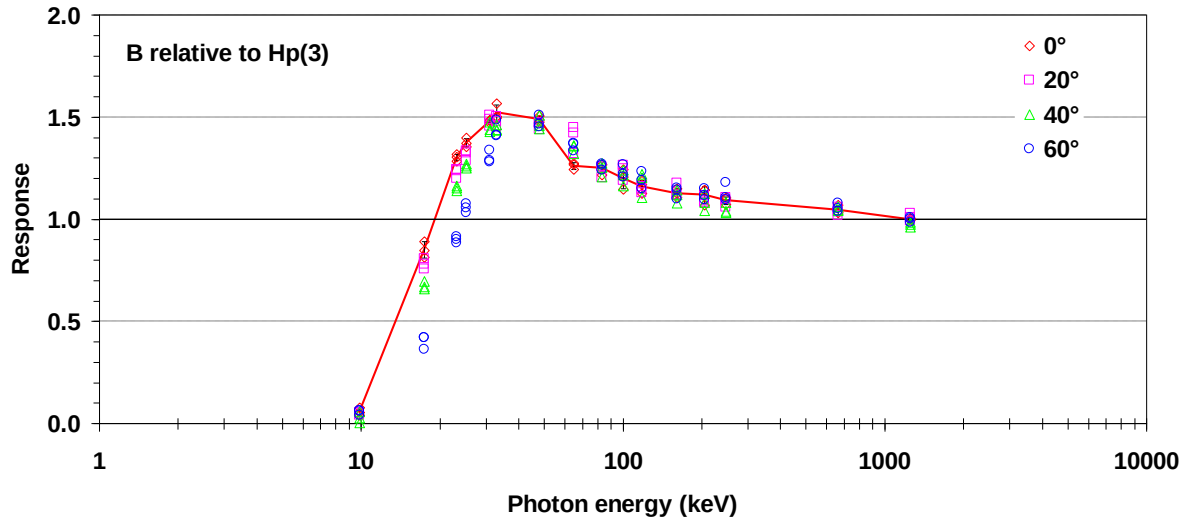

Figure 1: Response of the B-position detector of the NRG whole body photon dosemeter to $H_p(3)$, on the ISO water slab phantom. The solid line connects the mean values for normally incident radiation.

Figure 2 The eye lens dosemeter developed in the ORAMED project

Although these results were encouraging, some obvious improvements were considered to be desirable. Firstly, the NRG whole body dosemeter was not designed to wear close to the eye. Secondly, the TLD material used shows an inherent over-response for the lower photon energies, which can only compensated by thicker filters, causing the energy-threshold to be increased. Thirdly, the calibration phantom used in the type test doesn't represent the human head very well with respect to the backscattered radiation. Therefore, NRG started new type tests with the dosemeter and the head phantom developed in the ORAMED project. The dosemeter was specifically designed to measure $H_p(3)$, contains a MCP-N detector, and is commercially available (figure 2).

Despite this revival of interest, a significant part of the radiation protection dosimetry community remains skeptic on the necessity for a complete metrological infrastructure around $H_p(3)$. As an example, the German Commission on Radiological Protection recommends not to put effort in measuring $H_p(3)$, but to use $H_p(0.07)$ as an acceptable estimate of the eye lens dose instead (SSK, 2010). During the course of this scientific debate, the question whether $H_p(3)$ will ever reach the health and maturity of its sister-quantities $H_p(10)$ and $H_p(0.07)$ remains unanswered as yet.

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