Ionizing radiation metrology in cancer radiation therapy

The function of metrology, the science of measurement, is fundamental to the correctness of the therapeutic dose delivered to the patients and to the improvement of the cure rate. The standardization of the clinical dosimetry worldwide is achieved through the development of adequate standard instruments and of traceable dosimetry chains, which act as unbroken link between primary and clinical measurement. The paper deals with the main recent scientific achievements of the National Institute for Ionizing Radiation Metrology of ENEA (ENEA-INMRI) in external beam radiotherapy dosimetry, in dosimetry for brachytherapy and in nuclear medicine. The ENEA-INMRI activities undertaken in the framework of recent European Research Projects, jointly carried out with other National Metrology Institutes in Europe, are briefly outlined. The development of the ENEA-INMRI national standards and the establishment of new metrological chains are part of the international effort towards the optimization of radiation therapy treatments. The ENEA-INMRI achievements described in the paper show to what extent the Italian ionizing radiation metrology is contributing to the worldwide fight against cancer

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La metrologia delle radiazioni ionizzanti nella radioterapia dei tumori

La metrologia delle radiazioni ionizzanti svolge un ruolo importante nel garantire l'accuratezza della misura della dose in ogni fase delle procedure radioterapiche messe in atto per il trattamento dei tumori. La funzione della metrologia, la scienza della misurazione, risulta fondamentale per la correttezza della dose terapeutica somministrata ai pazienti e il miglioramento delle percentuali di guarigione. La standardizzazione della dosimetria clinica su scala mondiale si ottiene attraverso lo sviluppo di adeguati strumenti campione e di catene dosimetriche riferibili, che fungano da legame ininterrotto tra la misurazione a livello primario e quella a livello clinico. L'articolo presenta i principali e più recenti risultati scientifici dell'Istituto Nazionale di Metrologia delle Radiazioni Ionizzanti dell'ENEA (ENEA-INMRI) nella dosimetria per radioterapia con fasci esterni, nella dosimetria per brachiterapia e nella medicina nucleare. Vengono brevemente descritte le attività svolte dall'ENEA-INMRI nell'ambito di recenti progetti di ricerca europei svolti in collaborazione con altri istituti nazionali di metrologia europei. Lo sviluppo dei campioni nazionali dell'ENEA-INMRI e la creazione di nuove catene metrologiche fanno parte dell'impegno internazionale rivolto all'ottimizzazione dei trattamenti di radioterapia. I risultati ottenuti dall' ENEA-INMRI e descritti in questo articolo delineano in quale misura la metrologia italiana nel campo delle radiazioni ionizzanti riesca a contribuire su scala internazionale alla lotta contro il cancro

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According to most recent literature findings, in Europe in 2008 there was an estimate of 3.2 million cancer cases diagnosed (excluding non-melanoma skin cancers), 53% (1.7 million) occurring in men and 47% (1.5 million) in women. There were 1.72

million estimated deaths from cancer, corresponding to 56% (0.96 million) in men and 44% (0.76 million) in women (Ferlay et al 2010). In terms of the number of deaths caused per year, cancer ranks second in the European mortality statistic, behind cardiovascular diseases. Tumours can be eradicated by ionizing radiation irradiation. Approximately 5% of all cancer patients receive radiation therapy of some form (including external beam and brachytherapy), either alone or in combination with other treatment modalities such as surgery or chemotherapy (Delaney et al 2005). Hence, any improvement in the efficacy of radiation therapy will benefit a large number of patients. Radiation therapy has a firm scientific foundation and is used to kill cancer cells selectively or to keep them from proliferating. The accurate knowledge of the dose imparted to the tumour is fundamental in studies of biological effects of irradiation as well as in clinical radiotherapy practice. In fact, scientists and radiotherapists communicate with each other sharing information about absorbed dose levels that produce tumour control without causing severe injury to normal tissues, for a given treatment plan and irradiation technique. For an effective scientific communication, it is essential that these dose levels be based on SI-traceable and accurate measurements with a well stated uncertainty. By definition, clinical measurements are traceable if they can be related to a common national or international reference standard through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty. The dose imparted to cancer patients must be known within a narrow band of uncertainty to avoid either damage to the healthy tissue, resulting from exceeding internationally-agreed tolerance levels, or lack of tumour control, due to a too low dose delivered to the target volume. The general consensus is that a change in the delivered dose to the patient by more than 5% may cause a relevant change of the tumour control probability and may result in an increased healthy tissue complication probability (ICRU 1976, Andreo 2010). Radiation metrology, through the development of adequate primary and secondary standards and traceable dosimetry chains, plays a key role in ensuring the accuracy of the dose measurement in each step of the radiotherapy procedures and in standardizing the clinical dosimetry worldwide. The different types of radiation and treatment modalities used in radiotherapy are constantly evolving and this continuously gives rise to new problems in ensuring the traceability of measurements in clinical practice.

A precondition for a successful implementation/improvement of radiotherapy techniques is the availability of a sound metrological basis to the assessment of the administered dose. Today, this basis is well available in dosimetry for conventional external beam radiotherapy where metrology has been deeply involved and has had time to establish a robust global network of primary standards of absorbed dose to water, the quantity of interest in all radiotherapy modalities. In the case of most recent and innovative therapeutic methods in the fight against cancer, like Intensity Modulated Radiation Therapy (IMRT), brachytherapy, and molecular radiotherapy, there is still an urgent requirement for a solid underpinning metrology. In these areas it is necessary to develop all the steps of specific dosimetry chains more effectively, in order to optimize the dose given to the patient receiving radiotherapy. This requires establishing dedicated primary and/or secondary standards, calibrating specifically-designed reference, and field instruments up to special procedures for the verification, at clinical level, of the dose in and around the tumour.

The ENEA National Institute for Ionizing Radiation Metrology (ENEA-INMRI) is strongly and constantly involved in metrological activities for cancer radiation therapy. It has developed new primary and secondary national standards of absorbed dose to water, and has established metrological and dosimetry chains traceable to these standards. Since the eighties, ENEA-INMRI has been giving a contribution to the development and the publication of guidelines of good practice measurement at national and international level (AIFB 1988, Piermattei et al 1997, Andreo et al 2000). Since 2007, ENEA-INMRI has been participating in the research projects of the European Metrology Research Programme (EMRP) funded

by E.C. and coordinated by the European Association of National Metrology Institutes (EURAMET[1]). In the 2008–2011 period, within the EU Seventh Framework Programme, ENEA-INMRI participated in the two EURAMET-EMRP joint research projects of major interest for radiation therapy: the project "External Beam Cancer Therapy" with short name EBCT, and the project "Increasing Cancer Treatment Efficacy Using 3D Brachytherapy" with short name Brachytherapy (Ankerhold and Toni 2012). EMRP is a long-term programme and ENEA-INMRI is currently participating in other newly-started projects and forthcoming ones.
In the following, the roles of metrology in the main fields of radiation therapy are described and the ENEA-INMRI contributions in ensuring the traceability of clinical measurements to the national and international standards and in the advancement of metrology in the different treatment modalities are presented.

External beam radiotherapy

External beam radiotherapy (EBT) is the most common form of cancer treatment in which the ionizing radiation is targeted at the tumour site from outside the patient's body. EBT is carried out mainly by means of gamma rays, x-rays and electrons, even if in recent years a few radiotherapy centres have been using protons and heavy ions with promising therapeutic results. Therapeutic photon and electron beams are generated by three types of equipment: cobalt units, linear accelerators and superficial and orthovoltage x-ray units. Cobalt units use the ^{60}Co radioisotope to produce gamma-ray photons with an average energy of 1.25 MeV. Since the development of the first ^{60}Co teletherapy unit in the early 1950s, cobalt units had been the most widely used radiotherapy radiation source for many years, but during the last two decades their role has partly been replaced by the more versatile linear accelerator. Nowadays cobalt treatment is still important just in specific applications as stereotactic radiosurgery (*i.e.*, the Gamma Knife system). Commercially available medical linear accelerators produce x-rays and electrons with energy in the range from 4 MeV up to around 25 MeV. Megavoltage x-rays are generally used for treating deep-seated tumours (6-10 MV units are typically used for lung or brain treatments, while 15-18 MV units for pelvic and abdominal regions), while electron beams are useful for treating superficial lesions since the maximum of dose deposition occurs near the body surface. For electrons beams with nominal energies in the range from 4 MeV to 20 MeV, the treatment range is 1 to 5 cm. Superficial and orthovoltage units are similar to the diagnostic x-ray machines and produce x-rays (up to 300 kVp), used for treating skin cancer and superficial tumours.

Reference dosimetry

To perform a successful cancer treatment with external beams the irradiation must be carefully defined in such a way to deliver a suitable high absorbed dose to the target volume (i.e., the tumour), limiting the dose delivered to the healthy tissues as much as possible. The optimal treatment is obtained using specific software (Treatment Planning System, TPS) for calculating three-dimensional dose distributions starting from the patient's data and the beam characteristics. Thus the accuracy and reliability of measurements for the beam characterization are directly related to the success or failure of the radiation treatment. As a consequence, since the eighties considerable efforts have been made to improve the dosimetry accuracy starting from the beam calibration or measurements in reference conditions to the verification of treatment delivery. Primary standards, measurement techniques, and standardized measurement procedures have been developed and continuously improved to provide sound metrological bases to the dosimetry in EBT. Even if the absorbed dose to water, D_w, is the reference quantity for radiotherapy, the first standards developed and proposed as a reference were standards of the quantity air kerma. Then, several national and international dosimetry protocols were published to provide parameters and correction factors needed for deriving absorbed dose to water from air kerma (Andreo et al 1987, AIFB 1988). In the meanwhile, many national standards laboratories, including ENEA-INMRI, developed absorbed dose to water standards and this led to new dosimetry protocols with the advantage of reduced difficulties and uncertainties for the users at the radiotherapy centres (Andreo et al 2000, Almond et al 1999). In the current practice, EBT dosimeters are calibrated in terms of absorbed dose to water in a reference ^{60}Co beam in reference conditions (10 cm x 10 cm field size and 5 g cm^{-2} depth in water). Then dosimetry protocols provide standardized procedures and correction factors as a function of a beam quality specifier that allows to apply a ^{60}Co calibration coefficient in all types of external beams, except for orthovoltage x-rays for which calibrations are still performed in terms of air kerma. When applying procedures, parameters, and correction factors recommended in the dosimetry protocols, the 1 σ uncertainty in reference dosimetry of static broad beams used for conventional radiotherapy lies between 1% and 2%, therefore well within the stated limit of 2.5% (Andreo 2010).

ENEA-INMRI absorbed dose to water standard

D_w primary standards established by the National Metrology Institutes are based on different measurement techniques like water calorimetry, graphite calorimetry, and ionometry, hence forming a robust system of standards. The reference values of D_w obtained from the different standards are periodically compared to each other by means of international comparisons and the degree of equivalence among the national standards is registered in the Bureau International des Poids and Mesures (BIPM) data base (http://kcdb.bipm.org/default.asp). The D_w primary standard established at ENEA-INMRI for the ^{60}Co gamma radiation (Guerra et al 1996) is based on a graphite calorimeter (Figure 1) and on a conversion procedure that allows to derive absorbed dose to water from absorbed dose to graphite, D_g, measurements. Graphite is widely used in absorbed dose calorimetry thanks to its similarity to water as regards ionizing radiation interactions and its high temperature diffusivity. Moreover, graphite can be easily machined and this behaviour makes complex designs in calorimeter construction possible (Domen and Lamperti 1974, Domen 1987, Seuntjens and Duane 2009). The temperature rise in graphite due to irradiation is very small, 1.4 mK per Gy of delivered dose. The calorimeter temperature stability required for absorbed dose measurements is of about 10 μK per minute. The long-term stability of the ENEA-INMRI graphite calorimeter is 0.15% (1σ). The relative combined standard uncertainty in the absorbed dose to graphite reference value is 0.27%.

The procedure to convert the absorbed dose from graphite to water requires a graphite thick-walled ionization chamber (wall mass thickness 0.5 g cm^{-2}), acting as a transfer standard, and two phantoms, one made of graphite and one made of water. The thick-walled chamber is first calibrated in terms of absorbed dose to graphite in the graphite phantom with dimensions identical to the graphite calorimeter. Then the absorbed dose to water is derived from absorbed dose to graphite measured by the thick walled chamber in the water phantom (Figure 2). To achieve a correct dose transfer, different measurement points are chosen in graphite and in water in order to obtain similar radiation energy spectra, thus assuring that the energy response of the transfer chamber does not change when passing from calibration conditions in graphite to measu-

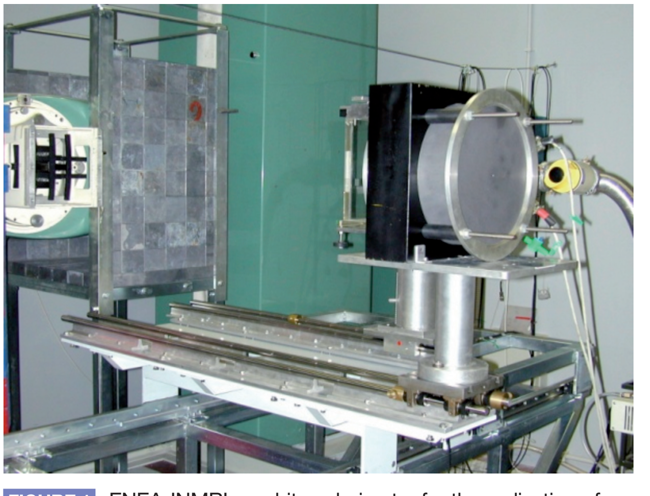

FIGURE 1 ENEA-INMRI graphite calorimeter for the realization of the absorbed dose to graphite unit in the reference ^{60}Co beam, for external beam radiotherapy

rement conditions in water. Since the first establishment of the ENEA-INMRI primary standard, considerable work has been done in order to improve its accuracy. At present, the relative combined standard uncertainty in the reference D_w value is 0.36%. The standard is periodically compared with the analogous standard of the BIPM and the current degree of equivalence to the worldwide D_w standards is shown in Figure 3 (Kessler et al 2010). Radiotherapy dosimeters are currently calibrated with the present standard at ENEA-INMRI. The dosimeter calibration coefficients are provided with a relative combined standard uncertainty of 0.6%, hence allowing clinical dosimetry in compliance with the international accuracy requirements (Andreo et al 2000).

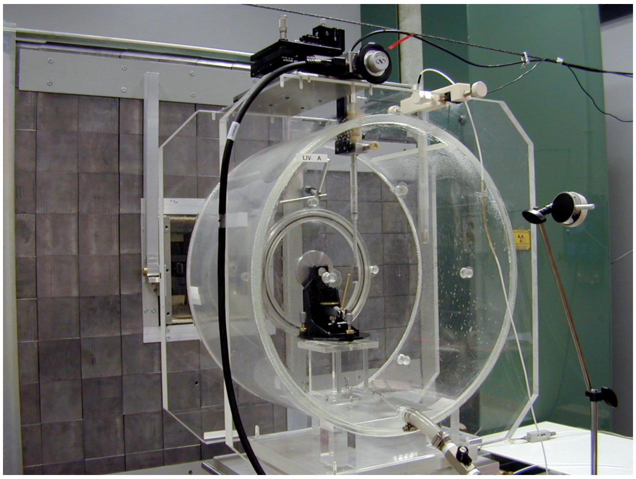

FIGURE 2 Water phantom and thick-walled transfer ionization chamber for the realization of the absorbed dose to water unit at ENEA-INMRI in the reference ^{60}Co beam, for external beam radiotherapy

Dosimetry in small photon beams

Over recent years new therapeutic modalities like Intensity Modulated Radiotherapy (IMRT), helical Tomotherapy, and Cyberknife radiosurgery have been introduced in the clinical practice. All these techniques allow the delivery of dose distributions with a high-dose area matching the tumour shape, steep dose gradients in the border area, and low-dose areas in the surrounding healthy tissues and neighbouring organs at risk. These complex dose distributions are produced by superimposing a large number of small radiation fields (down to 0.5 cm x 0.5 cm), impinging on the patient from different directions. The treatment plans required for these irradiations are very complex and need to be verified by measurements as a matter of patient protection.

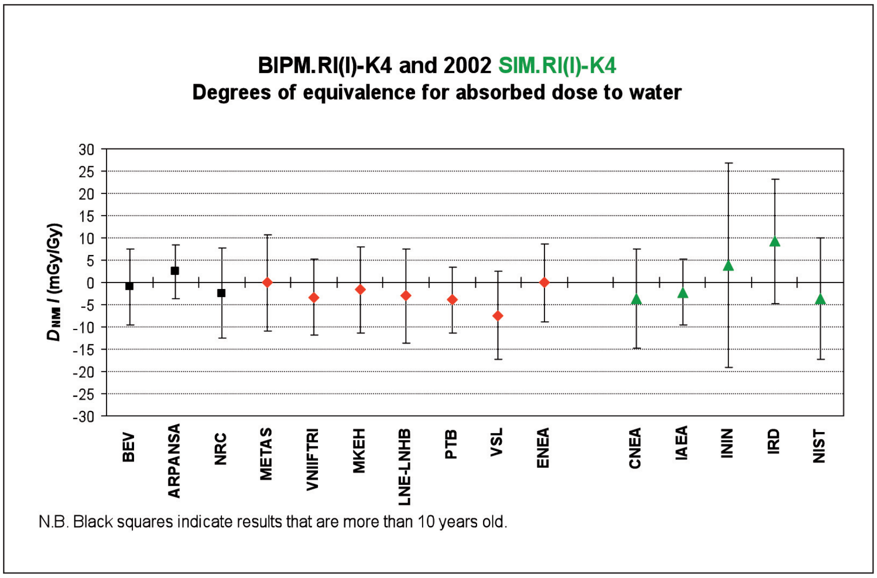

FIGURE 3 Graph of the degrees of equivalence of the absorbed dose to water standards (established by worldwide National Metrology Institutes), for external beam radiotherapy, with the "Key Comparison Reference Value". Most of the results agree within 5 mGy/Gy, that corresponds to a relative deviation of 0.5%

However, the current dosimetry protocols cannot be rigorously applied for this aim. These protocols rely on reference ionization chambers (volume larger than 0.1 cm^3) calibrated in a reference beam, on clinical measurements performed in reference conditions (*i.e.*, 10 cm x 10 cm field size) and on beam quality specifiers which relate the beam energy to the dosimeter response (*i.e.*, $TPR_{20,10}$ for megavoltage x-rays and R_{50} for high energy electrons according to the IAEA-TRS-398 (Andreo et al 2000)). Due to their large sensitive volume, ionization chambers are not suitable for measurements in radiation fields smaller than few centimetres. Moreover, in photon beams with small fields the loss of lateral equilibrium of charged particles makes the beam characteristics (*i.e.*, energy and angular distributions) different from those in the reference field size. Therefore the validity of parameters and correction factors given by the dosimetry protocols is not ensured. Additionally, some new machines like Tomotherapy and Cyberknife do not allow establishing the recommended reference conditions (i.e., field size 10 cm x 10 cm) for the beam calibration. As a consequence, the beam quality specifier cannot be determined in compliance with the protocol procedures and this poses a problem in selecting the appropriate beam quality correction factors.

The development of measurements procedures for the determination of absorbed dose in small and irregular photon beams has been one of the major objectives of the project "External Beam Cancer Therapy" (see introduction). New primary standards of absorbed dose to water based on graphite and water calorimeters have been established in field sizes down to 2 cm x 2 cm, which is the limit of applicability of the calorimetric technique, due to the large lateral heat dissipation. By the aid of these new standards, several types of dosimeters like alanine, diamond detector, and small-volume ionization chambers have been investigated for their applicability as reference dosimeters down to 2 cm x 2 cm field size. To extend the dosimeters investigation to smaller fields, Monte Carlo simulations were made. At ENEA-INMRI, a new synthetic diamond detector fabricated at the Rome University "Tor Vergata" has been investigated and demonstrated suitable to be used as calibrated dosimeter in small photon beams (Pimpinella et al 2012b). Among the detectors studied, only the new diamond detector and alanine dosimeters were found capable to perform dose measurements in photon beams with field sizes down to 1 cm x 1 cm. The two types of dosimeters have similar accuracy (around 1%); the alanine dosimeter has the advantage of an energy-independent response, while the diamond dosimeter has the advantage of a real-time reading and the smallest sensitive volume (Pimpinella et al 2012a).

Nevertheless, the investigation of the dosimeters response in small fields revealed that accurate absorbed dose measurements in extremely small fields (less than 2 cm x 2 cm) are possible only if the beam distribution over the detector volume can be also accurately measured, in order to correct the signal for the effect of non-uniform detector irradiation. In very narrow fields, this correction can be large even for detectors as small as alanine dosimeters (diameter of 5 mm) and diamond detectors (diameter of 2 mm). Therefore, a dosimetric system suitable for dosimetry in extremely small field sizes should include both an adequate point-like dosimeter (*i.e.*, diamond or alanine) for central axis measurements and an accurate two-dimensional detector for field profile measurements. Moreover, a new beam quality specifier suitable to describe, even in small fields, the beam characteristics which affect the dosimeter response is needed in order to compare the detectors response in photon beams with small field sizes produced by different accelerators. Both aspects are going to be studied at ENEA-INMRI in the framework of a new EURAMET-EMRP project (Metrology for radiotherapy using complex radiation fields), that will start in June 2012. The research activity planned for the new project is also addressed to give metrological basis to the procedures applied for the verification of treatment planning systems.

Dosimetry for high-dose-per-pulse electron beams

In recent years, the use of mobile electron accelerators dedicated to intra-operative radiotherapy (IORT) has been increasing in Italy. IORT is a technique where a single fraction of high dose of radiation is applied to the tumour in the operating room during surgery. As a consequence, mobile accelerators specifically designed for IORT are characterized by a very high dose per pulse (higher than 10 mGy per pulse), that allows the delivery of the prescribed dose of about 10-25 Gy in a very short time (less than 1 min). The dosimetry of such beams requires particular care when performed by ionization chambers, mainly due to the possible errors in determining the correction factor that takes into account the ion recombination in the chamber air cavity (Laitano et al 2006). Moreover, the IORT specific collimator systems give rise to a component of scattered electrons in the useful beam larger than in the conventional beams. Hence, for accurate IORT dosimetry the influence of scattered electrons component on the dosimetric parameters needs to be evaluated. To overcome this inconveniences at ENEA-INMRI, first, a calibration service to allow in-situ calibration of IORT beams has been developed, and following, dosimetric parameters specific for the IORT accelerators have been determined simulating the electron beams by Monte Carlo (Pimpinella et al 2007a, 2007b). The calibration service is based on ferrous sulphate reference dosimeters produced at ENEA-INMRI. The dosimeter response is independent of dose-rate up to 1 Gy per pulse, while all other correction factors have been determined by Monte Carlo simulations. The combined standard uncertainty on D_w measurements by ENEA-INMRI reference dosimeters is 1.6%. Up to now the dosimeters have been applied for the calibration of about forty IORT accelerators operating in the Italian radiotherapy centres.

Brachytherapy

Brachytherapy (BT) is a radiation therapy modality in which sealed radioactive sources are placed inside or at very short distances from the tumour to deliver high radiation dose locally with a rapid dose decrease in the surrounding healthy tissues. BT is performed using both low-dose-rate (LDR) source implants, *i.e.*, with prescription dose rate from 5 to 20 mGy/min, and high-dose-rate (HDR) sources, *i.e.*, with prescription dose rate of 200 mGy/min or higher. Historically, BT developed in the last century through the use of sealed 226Ra needles. In the 1950s, the availability of the artificially produced radionuclides (*e.g.*, ^{125}I, ^{192}Ir, ^{137}Cs, ^{60}Co, ^{198}Au, ^{103}Pd) gave rise to an increased interest in BT, also with the introduction, in 1965, of the remote afterloading technology, in which the BT sources are moved to the treatment position in the patient by an automatic mechanism with remote control, eliminating the exposure of the medical staff due to the source handling. Accurate metrology of the radioactive sources and developments in the computer technology were fundamental in the transition from dose estimations based on generic tables referred to typical BT sources implants to computer-calculated and personalized 2D and 3D dose distribution determinations. Nevertheless, differences in the clinical practice and in the related dosimetry still exist in the various countries and modern BT calls for continuous research in radiation metrology.

According to a recent survey (Guedea et al 2007, Guedea et al 2010), about 10% of the radiation therapy treatments is made with BT, and most BT interventions are for gynaecological tumours, followed by prostate, breast, lung/bronchus, and oesophagus tumours.

Since 1985, the reference quantity in BT has been the reference air-kerma rate, $\dot{K}_R$ (ICRU 1985) or the air kerma strength, S_k ((Nath et al 1995). The primary standards were based on cavity and free-air ionization chambers for the measurement of the quantity air-kerma rate. Starting from this quantity, the absorbed dose rate to water is calculated using a formalism established in 1995, based on both Monte Carlo-calculated and experimental conversion factors from $\dot{K}_R$ (or S_k) to absorbed dose rate to water determined at 1 cm distance from the source, $\dot{D}_{w,1\,cm}$ (Nath et al 1995, ICRU 2004). This conversion is based on the dose rate constant, Λ, *i.e.*, the ratio between $\dot{D}_{w,1\,cm}$ and the reference air-kerma rate $\dot{K}_R$ (or S_k). The use of Λ introduces a large uncertainty into the determination. Following this procedure, the uncertainty on the reference value of $\dot{D}_{w,1\,cm}$, is of about 5% (1σ) (Rivard et al 2004).

Historically, in 1995 ENEA-INMRI established the first

Italian primary standard of BT reference air-kerma rate and, in 1997, gave a contribution in drafting the Italian dosimetry protocol for dosimetry in BT, based on detector calibrations in terms of $\dot{K}_R$ (Piermattei et al 1997). The metrological and dosimetry chain based on $\dot{K}_R$, via the formalism described in the AAPM Task Group 43 Reports (Rivard et al 2004, Rivard et al 2007), is robust and reliable. Its limitations lie in the relatively large uncertainties that are inherent in the conversion procedure from $\dot{K}_R$ measurement to the evaluation of $\dot{D}_{w,1\,cm}$. A metrological chain based on absorbed dose to water standards will allow BT to satisfy the uncertainty requirements of other radiation treatment modalities.

To these ends, the European project "Brachytherapy" was carried out with the aim of reducing the uncertainty in the measurement of $\dot{D}_{w,1\,cm}$ below 2% (1σ). New BT primary standards were developed, able to directly measure $\dot{D}_{w,1\,cm}$ without the need of conversion procedures, starting from a different physical quantity and based on factors introducing large uncertainty components. The National Metrology Institutes of ten European countries were involved in the project.

ENEA-INMRI took part in this project, as leading Institute, by developing new D_w primary standards for LDR BT based on ionometry (see section 3.1) and for HDR BT based on calorimetry (see section 3.2). Furthermore, ENEA-INMRI contributed to the establishment of a new metrological chain for the traceability of clinical measurements to absorbed dose to water primary standards. These aspects are crucial to the 5% (1σ) target uncertainty in the determination of the D_w delivered to a patient.

New primary standards for the characterization of the BT sources in terms of D_w and the establishment of the metrological chains are the bases for using, at clinical level, field instruments calibrated in terms of D_w instead of reference air kerma. A metrological chain based on D_w standards is therefore expected to reduce the uncertainty of the therapeutic dose delivered to BT cancer patients.

LDR Brachytherapy

As a part of the project 'Brachytherapy', ENEA-INMRI developed a new primary standard measuring $\dot{D}_{w,1\,cm}$ due to LDR BT seeds emitting low energy photons. This standard is based on a large-angle, variable-volume (LAVV-1) chamber in graphite phantom (Figure 4). For the realization of the $\dot{D}_{w,1\,cm}$ unit, a Monte Carlo-based procedure was developed to convert pairs of measurements of air-kerma in finite air volumes to graphite-kerma first (in the absence of air) and to D_w later. The method, and the measurements made as a part of the development of the new ENEA-INMRI LAVV-1 standard, have already been described elsewhere (Toni et al 2012). BT LDR seeds, containing ^{125}I and manufactured by Bebig, were characterized in terms of $\dot{D}_{w,1\,cm}$ against the ENEA-INMRI LAVV-1 standard with a combined uncertainty of 2.6% (1 σ). In parallel, to link the new ($\dot{D}_{w,1\,cm}$) and the old ($\dot{K}_R$) reference quantities, the radioactive seeds were also characterized in terms of $\dot{K}_R$, and using the above mentioned protocol for the conversion, independent $\dot{D}_{w,1\,cm}$ values were obtained via the existing metrology. The $\dot{D}_{w,1\,cm}$ values obtained by the two methods were consistent within the experimental uncertainties, but the uncertainty in the direct determination of $\dot{D}_{w,1\,cm}$, with the new standard, was significantly reduced from 5.0% (1 σ) to 2.6% (1 σ). Once the new standard was developed, ENEA-INMRI also established a metrological chain based on the above mentioned LDR primary standard and two high-stability well-type ioniza-

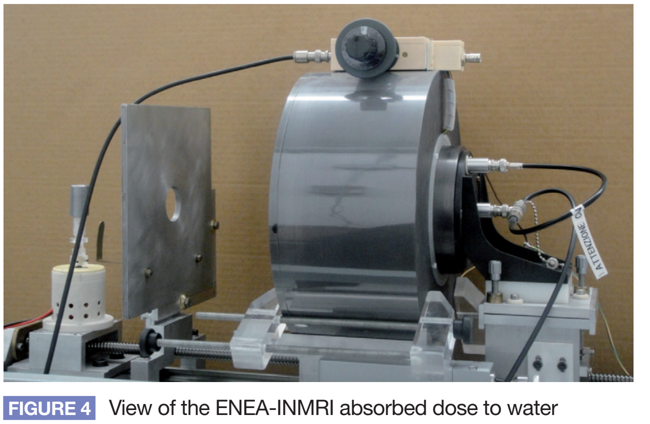

FIGURE 4 View of the ENEA-INMRI absorbed dose to water standard for low dose rate brachytherapy: the large-angle, variable volume graphite walled extrapolation chamber on the right, and the rotating source holder, on the left

tion chambers, acting as secondary and travelling standards, respectively. Using this newly developed metrological chain, the end-user in a radiotherapy centre can characterize each BT ^{125}I seed, before its use in the clinic, with an uncertainty in $\dot{D}_{w,1\ cm}$ lower than 2.8% (1 σ).
The dose rate constant Λ for the ^{125}I Bebig IsoSeed® I25.S16 LDR source was experimentally determined at the ENEA-INMRI (1.015 10^4 with an uncertainty of 2.5%, 1σ), considerably lower than the uncertainty in the currently accepted measured value of Λ (1.012 10^4, with an uncertainty of 4.8%, 1σ) (Rivard et al 2004).

HDR Brachytherapy

In the framework of the project 'Brachytherapy', ENEA-INMRI has developed a graphite calorimeter as primary standard for the absolute measurement of D_w, for HDR ^{192}Ir sources. The graphite calorimeter was designed to measure the absorbed dose to graphite, D_g, according to the operational definition of the quantity D_g, by determining the energy released by the radiation in a known mass of graphite (J/kg). The absorbed dose to water was then obtained by a conversion factor from D_g to D_w that was determined by Monte Carlo calculations. The main feature of the graphite calorimeter developed at ENEA-INMRI is that the ^{192}Ir source is inserted inside the detector so that the annular sensitive volume surrounds the source. The calorimeter consists of three annular graphite bodies with cylindrical symmetry around the source axis (Figure 5). The measurement method and the design of the new standard have already been described elsewhere (Guerra et al 2012).
The calorimeter was irradiated, using a ^{192}Ir MicroSelectron® HDR V2 source. D_w measurements were performed in the quasi-adiabatic mode of operation. The D_w measurements showed a reproducibility of about 1% (1σ). The combined standard uncertainty on the value of $\dot{D}_{w,1\ cm}$, was 1.4% (1σ), lower than the uncertainty in $\dot{D}_{w,1\ cm}$ determined on the basis of the quantity $\dot{K}_R$ (3%, 1σ). The dose rate constant Λ for the ^{192}Ir MicroSelectron® HDR V2 source was experimentally determined with an uncertainty of 1.8% (1σ), lower than the uncertainty associated to the few existing experimental determinations or the calculated values of Λ typically 3.0% and 2.1%, respectively (1σ) (DeWerd et al 2011).
The experimental results on D_w and Λ were highly consistent with the available literature data and provided the evidence of a considerable agreement at ENEA-INMRI between D_w determined by the ionometric method that starts from the $\dot{K}_R$ standard (old procedure), and D_w directly determined by the new calorimetric standard (new procedure).

Nuclear medicine and molecular radiotherapy

In the near future, metrology is likely to have a key role even in molecular radiotherapy (MRT), also called targeted radionuclide therapy. MRT is a novel therapeutic approach performed in nuclear medicine departments where a radiopharmaceutical is systemically administered to the patient. In contrast to chemotherapy, wherein all proliferating cells are affected, MRT is founded on the ability to identify or synthesize radionuclide carriers that recognize and bind to tumour-associated target molecules, thus delivering radiation to only those cells that express cancer markers.

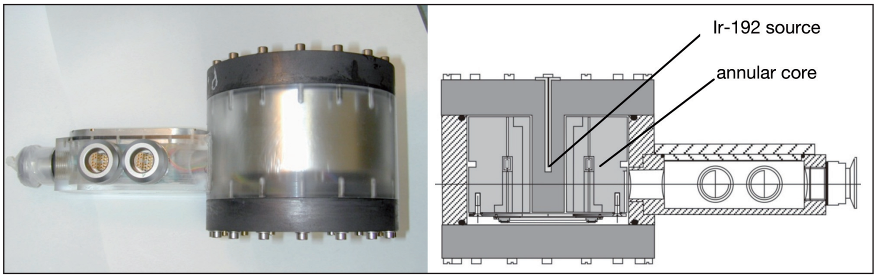

FIGURE 5 Lateral view and schematic section of the graphite calorimeter, the ENEA-INMRI absorbed dose to water standard for high dose rate brachytherapy. The annular core diameter is 50 mm. The PMMA housing external diameter is 130 mm. The external height is 105 mm

The treatment is based on the administration of a measured activity of radiopharmaceutical in a form that can be selectively taken up in the tissue to be treated. Nevertheless, it is clear that, for a given administered activity, the quantity taken up (and hence the therapeutic radiation dose to the tissue) varies widely among individuals because of unavoidable physiological and physical differences. Recent research indicates the absorbed dose differences range can be up to 2 orders of magnitude (Flux et al 2010). As a consequence, widespread use and development of new radiopharmaceuticals is currently hampered because the effectiveness on individuals is not well determined by the administered activity.
Furthermore, despite recent research and new technology developments have allowed estimates of radiation doses on individual patients both to tumour areas and normal tissues, there has been almost no adoption of these methodologies into routine clinical MRT practice. The reasons are many, but mainly because the methodology is difficult, there is no standardization of procedures, and there is no objective means of predicting how much difference individual patient dosimetry would make to treatment outcome.
For the above mentioned reasons, when compared with conventional external beam radiotherapy, in which individual patient dosimetry is controlled according to agreed protocols and there is full traceability to primary standards, it is evident that MRT is urgently in need of metrological support in order to bring this dosimetry practice up to an acceptable standard.

The ENEA-INMRI research activities in nuclear medicine

A wide range of γ, β^+ and/or β^- emitter radionuclides are currently used in nuclear medicine, both for diagnostics and for therapy, to target specific diseased tissues and physiological processes.
Radionuclide calibrators are used both at clinical level, to measure the activity of the radiopharmaceutical before its administration to the patient, and at the radiopharmaceutical production centres, to measure the radionuclide activity before its delivery to the end-user (public and/or private nuclear medicine departments). These instruments need to be calibrated using proper radioactivity standards in accordance with the recommendations of the European Pharmacopoeia.
Since 2005, the ENEA-INMRI has started an intensive research program in the field of radionuclide metrology to standardize short-lived radionuclides used in medical applications.
For this purpose, new primary standards of β^+ emitters, as ^{18}F used for diagnostic (Capogni et al 2006), and β^-/γ emitters, as ^{64}Cu (Capogni et al 2008), ^{177}Lu, ^{124}I used both for therapy and diagnostic, were developed by ENEA-INMRI by using absolute methods for radioactive measurements, like the $4\pi\gamma$ integral counting method based on a well-type NaI(Tl) 5''x 5'' detector and the $4\pi\beta$ Liquid Scintillation Spectrometry Method with ^{3}H Standard Efficiency Tracing (CIEMAT/NIST method).
The increasing request of new radiopharmaceuticals for diagnostic and radiation therapy has led to the intensification of research activities towards new measurement methods and novel detectors for accurate activity measurements of beta-emitters radionuclides. The Triple-to-Double Coincidence Ratio (TDCR) absolute method has been recently introduced at ENEA-INMRI for standardizing pure β radionuclides, with particular attention to those used in nuclear medicine.
Through the new developed primary standards, two re-entrant ionization chambers (fixed and portable), have been calibrated with an uncertainty lower than 2%. The chambers have been used to calibrate activity measurement instruments of the end-users thus assuring the traceability chain to the primary standards maintained at ENEA-INMRI.
In many cases, due to the short half-life of the nuclides used in diagnostic applications, the portable ionization chamber, shown in Figure 6, has been used as secondary standard measuring instrument for calibrating the instrumentation of the Nuclear Medicine Department or the radiopharmaceutical production centers *in situ*.
Figure 7 shows the network of Italian radiopharmaceutical production centers and nuclear medicine

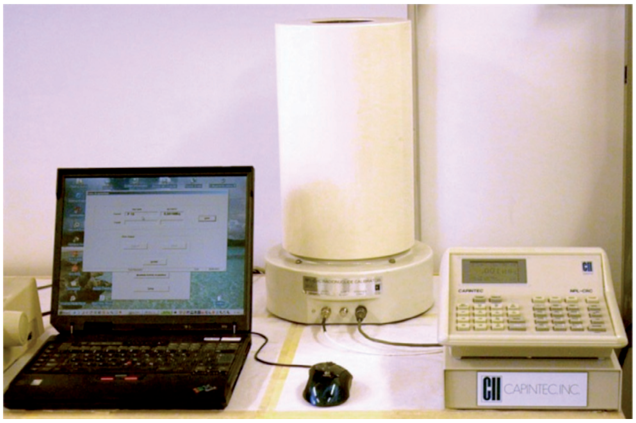

FIGURE 6 The ENEA-INMRI Secondary Standard Measurements Systems for nuclear medicine radionuclides, based on a well-type ionization chamber, current measuring system and PC controller

departments where the instruments used for activity measurements of short-lived radionuclides (^{18}F, ^{64}Cu, ^{124}I) have been calibrated by ENEA-INMRI.

The forthcoming EURAMET-EMRP project “Metrology for molecular radiotherapy”

Based on its competence, ENEA-INMRI is currently participating in the challenging EURAMET-EMRP project “Metrology for molecular radiotherapy” (denoted as JRP-h13 MetroMRT) that aims at developing the background metrology to support routine individual dosimetry for MRT patients. The primary aim of the project is the validation of a practical measurement methodology that can be adopted widely in clinical departments, and which is supported both by metrology laboratories in the provision of calibration and verification services and by the consensus of the nuclear medicine community.

ENEA-INMRI will be actively involved in the development of a primary activity measurement method based on the Čerenkov emission in aqueous solutions using conventional triple-to-double-coincidence-ratio (TDCR) Čerenkov apparatus for the standardization of high-energy beta-emitting radiopharmaceuticals. By this technique (Kossert 2010, Bobin et al 2010) the activity measurements are carried out directly with aqueous solutions, avoiding mixing with the scintillating cocktail, hence reducing possible chemical instabilities and limiting the handling of radioactive sources. The Čerenkov emission is also characterised by a threshold effect that can be used advantageously to naturally discriminate the standardised radionuclide from low-energy β and/or α impurities in the radioactive solution.

The need for this task arises from the fact that most radionuclides used as radiopharmaceuticals for molecular radiotherapy applications are high-energy-beta emitters chemically linked to specific organic molecules (antibodies, peptides) and dissolved in an aqueous solution. These radiopharmaceuticals (among which ^{90}Y microspheres used for selective internal radiation therapy of liver cancer) raise specific standardization problems, both for primary measurements and for transfer calibration and measurement at the hospital that need to be addressed.

FIGURE 7 Map of the radiopharmaceutical production centres and nuclear medicine department in Italy calibrated by the ENEA-INMRI

Within the project, ENEA-INMRI will also be involved in a feasibility study on the development of an absorbed dose primary standard for radionuclides. In fact, at present the reference quantity for dosimetry in molecular radiotherapy is the activity and absorbed dose values for reference geometries are generally derived from activity by calculations. The idea behind the development of a primary absorbed dose standard for radionuclides is to introduce the absorbed dose to water for a given radionuclide as reference quantity. The reference geometry will be a water-filled volume where the radionuclide is distributed. Although for pure beta emitters the absorbed dose can be calculated by the decay scheme, the conversion procedure does not allow a traceable dose verification and introduces an additional uncertainty component in the absorbed dose evaluation. Furthermore, the development of a primary standard is of utmost importance since: 1) molecular radiotherapy often uses non pure beta-emitters radionuclides which do not allow accurate dose calculation from activity 2) current absorbed dose measurements from radionuclides are performed using dosimeters which are calibrated against radiation sources other than the sources the dosimeter will be exposed to. The availability of a reference absorbed dose standard for selected radionuclides, *i.e.*, of a dosimeter calibration in terms of the same physical quantity to be measured, is expected to reduce the calibration and measurement uncertainty.

The outcomes from the forthcoming MetroMRT project will hopefully enable personalized treatment based on patient-specific treatment planning which will have a direct and potentially significant benefit on patient treatment. Within a dedicated programme of dissemination, the Metrology Institutes participating in the project will work with the clinical community to achieve widespread implementation.

Conclusions

Approximately 50% of all cancer patients receive radiation therapy over the course of their illness. Radiation metrology plays a key role in improving the accuracy of the dose delivered to cancer patients worldwide, helping in the fight against cancer. In fact, the better the accuracy in dose delivery to tumour, the higher the likelihood of cancer cure.

The ENEA-INMRI is strongly and constantly involved in the advancement of metrology in cancer radiation therapy. The development of the ENEA-INMRI national standards and the establishment of new metrological chains are part of the international effort towards the optimization of radiation therapy treatments. This can be achieved using the absorbed dose to water, the quantity of interest in radiotherapy, as the reference quantity for measurement traceability in all radiation therapy treatment modalities. The consistency between the reference quantity realized at the National Metrology Institutes and the quantity measured at clinical level will reduce the uncertainty on the therapeutic dose delivered to the cancer patients and contribute to the improvement of the cure rate.

notes

1 EURAMET is a Regional Metrology Organisation of Europe. It coordinates the cooperation of National Metrology Institutes (NMI) of Europe in fields like research in metrology, traceability of measurements to the SI units, international recognition of national measurement standards and related Calibration and Measurement Capabilities of its members. EURAMET is responsible for the elaboration and execution of the European Metrology Research Programme, known as the EMRP, which is designed to encourage collaboration between European National Metrology Institutes and partners in industry or academia.

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