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RESEARCH ARTICLE

# A Compact Neutron Generator for the Niort® Treatment of Severe Solid Cancers

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**ABSTRACT**

In the last four years, TheranostiCentre S.r.l., Berkion Technology LLC and ENEA have patented and fabricated a first prototype of a Compact Neutron Generator (CNG) currently under testing in the ENEA laboratories. Besides the usual applications in the field of materials irradiation, this CNG - producing neutrons of 2.45 MeV energy through the deuterium-deuterium (DD) fusion reaction - was conceived for the neutron irradiation of the solid cancer's tumour bed by means of the Intra-Operative Radiotherapy (IORT) technique, the so-called neutron-IORT (nIORT®). The DD-CNG is self-shielded and light-weight (~120 kg) making possible its remote handling by a robotic arm. Accurate Monte Carlo simulations, modelling the CNG and the "open wound" biological tissues near its irradiation window, demonstrated that the apparatus operated at 100 kV-10 mA supplies a neutron flux ~$10^8$ $cm^{-2}$ $s^{-1}$ and can deliver equivalent dose rates ~2 Gy (RBE)/min. Hence, it can administer very high dose levels in limited treatment times.

This article briefly summarizes the main findings of this collaborative research study, the clinical rationales underpinning the nIORT® idea and the potential performances of the DD-CNG for the treatment of solid cancer pathologies. Indeed, the CNG can be installed in an operating room dedicated to nIORT® treatments, without posing any environmental and safety issues. Monte Carlo simulations have been carried out by envisioning the CNG equipped with an IORT applicator, that is an applicator pipe with a tuneable diameter to be inserted in the surgical cavity. By foreseeing the clinical endpoints of the standard IORT protocols, the irradiation performances for potential nIORT® treatments - obtained with an applicator pipe of 6 cm diameter - are here reported for different regimes: from 10 up to 75 Gy (RBE), that can be administered in a single session of about 4 to 30 minutes. Besides the dose peak in the centre of the tumour bed, the almost isotropic neutrons emission allows to irradiate its surroundings side-walls – usually filled by potential quiescent cancer cells – and therefore reducing the chances of local recurrences by improving the local control of the tumour. The rapid decrease in tissues depth of the dose profile (in few centimetres) will spare the neighbouring organs at risk from harmful radiations. Thus, the DD-CNG apparatus developed for nIORT® applications can potentially improve the resectability rate of a given neoadjuvant cancer treatment and, generally, could satisfy all five R's criteria of radiotherapy. Furthermore, in comparing with the current IORT techniques with electrons or low-keV Xrays, the nIORT® exploiting a high-flux neutrons beam of 2.45 MeV energy could lead to some significant clinical advantages due to its high linear energy transfer (~ 40 keV/mm as average) and significantly higher relative biological effectiveness (@16) than all other forms of ionizing radiation.

## Introduction

Several factors contribute to making the single-dose Intra-Operative Radiotherapy (IORT) very promising in cancer treatments. The IORT is a treatment technique which associates radiotherapy with surgery, that foresees the administration of a dose of radiation directly on the tumour surgical cavity, by irradiating the tissues that cannot be dealt by surgical resection after having removed the primary neoplastic mass. The direct visualization and the possibility to space out normal tissues allows one to maximize the dose to the tumour while minimizing the dose to normal tissues.

Conventionally, IORT is performed by low-energy (~50 KeV) X-rays [1] or by high-energy (~1 MeV) electrons. [2,3] Besides some significant advantages with respect to the External Beam Radiation Therapy (EBTR), the standard techniques still present some limitations. Indeed, tumour beds with significant topographic irregularities remain a therapeutic challenge with existing IORT technologies foreseeing a focused beam most reliable for flat tissue surfaces. It can be also noticed that electrons deliver the dose peak slightly below the tissues surface, low-keV X-rays deliver limited dose rates in a limited range of penetration (~1 cm), while more penetrating high-keV X-rays deliver relatively high dose levels also in healthy tissues (and organs) far from the tumour bed. These limitations could be overcome using the fast neutrons as ionizing radiation (IR) particles and adopting the so-called neutron-IORT (nIORT®) technique [4], invented by the TheranostiCentre S.r.l. company (TC, Italy) and further developed in collaboration with the Berkion Technology LLC company (BT, USA) and the Italian National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA).

In comparison with the conventional IORT and EBRT techniques with a focused irradiation beam, the major rationale for the nIORT® therapy is the diffuse spatial dose distribution of the neutrons IR in the tissues. Indeed, the almost spherically symmetric IR on the tumour bed has the advantages to be less sensitive to the margins of the surgery cavity and to the possible intra-tumour heterogeneity of the solid tumour cells since the neutron irradiator behaves like an IR "foam" within the cavity.

Differently from the Boron Neutron Capture Therapy (BNCT) exploiting thermal and epithermal neutrons to induce (n, α) reactions in boron carriers injected into patients [5,6,7], the fast neutrons interact directly and efficiently with the hydrogen nuclei, producing recoil protons that ionize the tissues. Monte Carlo simulations have shown that the nIORT® delivers on the tumour bed a fast-neutron IR with a high linear energy transfer (LET) [8] and a relative biological effectiveness (RBE) [9] significantly higher than all other IRs such as X-rays, electrons and protons, thus resulting very efficient in producing DNA double strand breaks (DSBs) of the cancer cells. [10] It is known that around 50% of the absorbed dose imparted by neutron collisions (between 0.1 and 70 MeV) is due the ionizing effect of elastically scattered recoil protons, mainly from hydrogen atoms present in water contained in living cells. The remaining 50% consists of 10%–35% from nuclear recoils (elastic neutron scattering) and up to 35%–40% from neutron-generated light ions (including deuterons, tritons, $^{3}He$ and alpha particles). Both the LET and RBE parameters are used to describe differences between the cell damaging due to photon and electron IRs (both with RBE = 1) and to other particles (e.g., neutrons, protons, ions). This variability can be explained by the fact that the RBE is not only dependent on the LET, but also on other physical factors, such as energy and dose rate of the irradiation beam, and biological factors, such as the type of tumor, the cell cycle stage and the oxygenation level. [11]

Another important aspect defining the effectiveness of radiotherapy is the repair of the DNA damage that is induced by the IR. [12] The DSBs are a determinant factor for the cell survival since they can lead to cell death if left unrepaired. While photon radiation induces mainly isolated lesions including single strand breaks (SSBs), fast neutron particles with high LET and RBE - inducing more highly localized DSBs and clustered DNA damage (CDD) - should lead to necrosis and apoptosis of the cancer cells. [13] Furthermore, the neutron field is less affected by the hypoxic nature of the tumour bed having an Oxygen Enhancement Ratio (OER) lower than other IRs. [14,15]

The research studies on nIORT® are currently ongoing with the experimental tests of the first prototype of the Compact Neutron Generator (CNG) designed, developed and built by TC, BT and ENEA. The irradiation performances of the CNG - producing neutrons of 2.45 MeV energy through the deuterium-deuterium (DD) fusion reaction – are going to be measured in a new equipped ENEA laboratory. The DD-CNG is self-shielded, light-weight (~120 kg, making possible its remote handling by a robotic arm) and can supply a neutron flux ~$10^{8}$ $cm^{-2}$ $s^{-1}$ at its irradiation window. The high flux level of fast neutrons with 2.45 MeV energy is particularly suitable for potential nIORT® treatments since:

1. the high LET (~ 40 keV/mm as average [16]) and high RBE (@16 [9]) IR are very effective in direct cancer cells killing;

2. the difficulties and limitations of the irradiation with fast neutrons [17,18,19] are overcome by the IORT modality;
3. some additional advantages could be obtained, in comparison with standard EBRT and IORT techniques with X-rays and electrons.

The main reasons of these potential benefits rely on: (i) the almost spatial isotropic irradiation field of the neutron beam, suitable also for irregular surfaces and acting as a sort of ionizing radiation "foam" filling the surgical cavity and allowing to kill potential quiescent cancer cells (QCCs); (ii) the dose peak released at the tissues surface and (iii) its strong decrease in few centimetres in tissues depth (because of the high LET), sparing the neighbouring organs at risk (OARs).

In parallel with the experimental characterisation of the first CNG prototype, a new DD-CNG design - suitable to be installed in an operating room (OR) dedicated to nIORT® treatments - is currently under development. The architecture of this new design envisages an applicator pipe to be used in IORT treatments that, via hard-docking, can be inserted close to - or in contact with - the tumour bed or the surgical cavity. The potential performances of the apparatus were evaluated through accurate Monte Carlo simulations by modelling the CNG, the IORT applicator and the "open wound" biological tissues in the surgical cavity around it, choosing the meaningful case of the breast cancer irradiation. The results of the simulations, here shown for the breast cancer case but easily generalisable to other tissues / tumour beds, demonstrated that the DD-CNG operated at 100 kV-10 mA can administer the dose targets defined by the standard IORT clinical protocols ~10 to 20 Gy (RBE) in treatment times of 4 to 9 minutes only.

The DD-CNG could be used also for dose escalation (beyond that which can be achieved with EBRT and standard IORT protocols) reaching very high doses in a single session, e.g. up to 75 Gy (RBE) in less than half an hour. This dose levels could be eventually delivered in the tumour volume without an excessive damage of the healthy tissues. Indeed, some preclinical studies have shown that normal tissue tolerates irradiation exceptionally well, e.g., in the spatially fractioned radiation therapy (SFRT), the peak dose reaches up to 100 Gy (RBE) in a single session. [20] Furthermore, initial pre-clinical studies have shown the so-called FLASH effect that, with dose rates far exceeding those currently used in clinical contexts, reduces radiation-induced toxicities for normal tissues whilst maintaining an equivalent tumour response. [21]

More generally, despite being a departure from the fractionated schemes of the EBRT, the nIORT® technique could satisfy all five R's criteria of radiotherapy, namely: reassortment, repair, reoxygenation, repopulation and radiosensitivity. [22] The idea of the authors is that the nIORT® can improve the Local Tumour Control (LTC) and should allow to the total disappearance of the primary tumour and neighbouring lymph node metastases without any local recurrence after the treatment. Therefore, the nIORT® could be adopted to consolidate neoadjuvant chemotherapies for successfully resected patients (with close or positive margins) or administered in unresectable patients without distant metastases.

**Background research studies**

Since 2018, the TC company and ENEA have conducted research studies finalized to the nIORT®. [4] The main effort was devoted to the development - from the conceptual design to the construction – of a DD-CNG conceived for the nIORT® treatment of the most severe solid cancer pathologies. This effort led to an international PCT patent filed in July 2021 and published on January 2023 by the World Intellectual Property Organization (International Publication Number WO 2023/281539 A1). [23] A prototype of this nIORT® apparatus titled NEUTRONBRUSH®, that is a 100kV – 10mA DD-CNG, has been designed and assembled by the BT company. Nowadays, the apparatus is under testing in a new equipped laboratory at the ENEA research centre in Brasimone (near Bologna, Italy), where an experimental campaign for the neutron beam characterization is about to start. [24] The pictures in Fig. 1 show some details of the DD-CNG – enclosed in a High-Density Polyethylene (HDPE) cylindrical column, having excellent properties in shielding neutrons – and the instrumentation adopted for the first experimental "cold" tests.

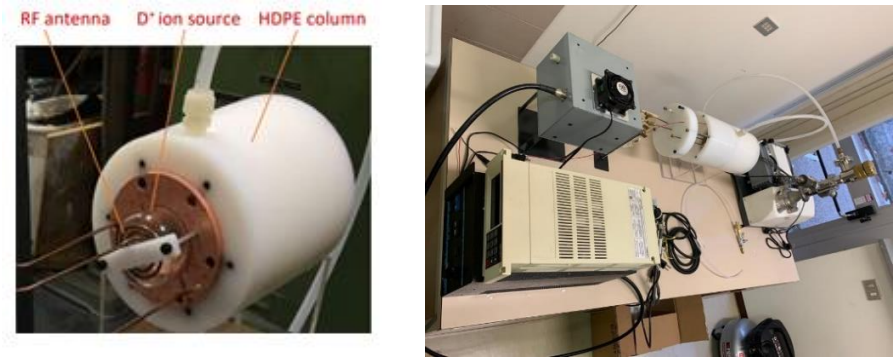


**Fig. 1**: CNG accelerator column (left); CNG with equipment for the firsts experimental tests (right).

The scheme on the left side of Fig. 2 summarizes the main features of the DD-CNG which consists, essentially of three main components: the ion source (i.e., plasma chamber with deuterium, a nonradioactive isotope of hydrogen), the acceleration column made with HDPE and the beam target electrode. [25] The positive deuterium ions (D+) - created in a RF-driven source chamber - are accelerated in the HDPE cylindrical hermetic void tube against a titanium (Ti) target where the DD fusion reaction occurs by generating neutrons of 2.45 MeV energy.

To optimise the DD-CNG performances in the view of potential nIORT® treatments, several Monte Carlo analyses were carried out by means of the Monte Carlo N-Particle (MCNP) ver. 6.1 code [26] coupled with the most up-to-date ENDF/B-VIII.0 nuclear data. [27] The MCNP studies [28] allow:

- to design the shield (for people, environment) surrounding the CNG and a collimator with an irradiation window from which to extract the neutron beam;
- to evaluate the dose rates in "open wound" biological tissues positioned at the irradiation window and, hence, to estimate the treatment times needed to administer the dose targets as defined by the standard clinical protocols.

The central frame of Fig. 2 shows a vertical section of the MCNP model of the CNG and surrounding shields, which are made of borated Polyethylene (PE+B) and an external layer of lead (Pb): the whole apparatus is a cylinder with about 30 cm in diameter and 40 cm in length. For simplicity, the CNG model does not include the ion source plasma chamber (in the back part of the acceleration column, see left drawing of Fig. 2) since the MCNP simulations start from the (almost isotropic) spatial distribution of the 2.45 MeV neutrons emitted from the Ti target on the opposite side of the CNG: thus, this model simplification has a negligible impact on the results at the irradiation window (e.g., flux) and into the biological tissues (e.g., flux and dose rate). A zoom on the MCNP model of the neutron collimator and the biological tissues near the irradiation window is also shown in the right frame of Fig. 2. By referring to the breast cancer treatment, the tumour bed in the surgical cavity (not covered by skin in correspondence of the irradiation window for the IORT modality) was surrounded by skin and muscle tissues, whose compositions were retrieved from Monte Carlo human phantoms' models in literature. [29]

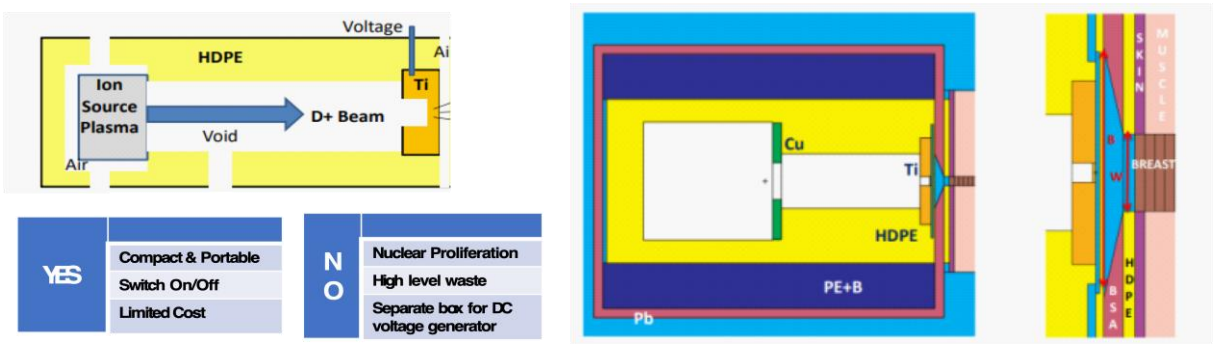


**Fig. 2**: Conceptual design of D+ ion-based CNG (left), vertical section of the MCNP model of the CNG, surrounding shields and biological tissues nearby the irradiation window (centre), zoom on the collimator and biological tissues models (right).

The basic idea in the nIORT® is to irradiate tumour beds "directly" with the monoenergetic 2.45 MeV neutrons emitted by the DD source, e.g., without moderating to epithermal or thermal energies as in the BNCT. [5,6,7] This high energy neutrons are very effective in cancer cells killing because of their high LET and RBE: @16 for 2.45 MeV neutrons. [9,30] This RBE value is significantly higher than of the proton in the Spread Out Bragg Peak (SOBP, estimated to be 1.1 to 1.2) and of the currently used 50 kV X-rays medical devices for IORT, which are 1.26 to 1.42 as measured in a phantom model. [31] The RBE was calculated by the MCNP code - through equation (1) reported in the following - starting from the neutrons' spectrum in biological tissues (peaked at 2.45 MeV) and the corresponding weighting factor. [9] Clearly, the RBE value (≃16 computed by MCNP code) for the nIORT® system will be validated experimentally by irradiating an anthropomorphic water phantom endowed with vials.

To briefly summarize the most significant MCNP results concerning the irradiated tissues, Fig. 3 shows the 2D map of the neutron flux distributions obtained with an irradiation window of 6 cm diameter: the distributions in depth (i.e., in breast and muscle tissues; left) and along superficial tissues (right) are reported. Fig. 4 shows the equivalent dose rate profiles again in depth (left) and along superficial tissues (right), together with the average value of the superficial dose rate in the whole irradiation window. The flux and the equivalent dose rate distributions shown in Figs. 3 and 4 were obtained by foreseeing the DD-CNG powered at 100 kV - 10 mA, which produces a neutron yield of 3.3 x $10^9$ $s^{-1}$ and a neutron flux ~8 x $10^7$ $cm^{-2}$ $s^{-1}$ at the centre of the irradiation window. [32]

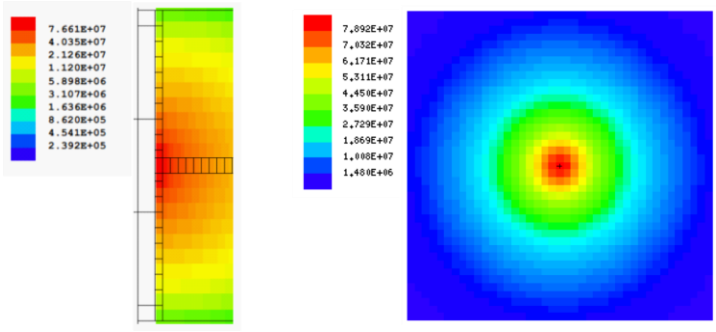


**Fig. 3:** MCNP results about the 2D neutron flux spatial distribution in depth (left) and along superficial tissues (right) obtained by a 6 cm window diameter.

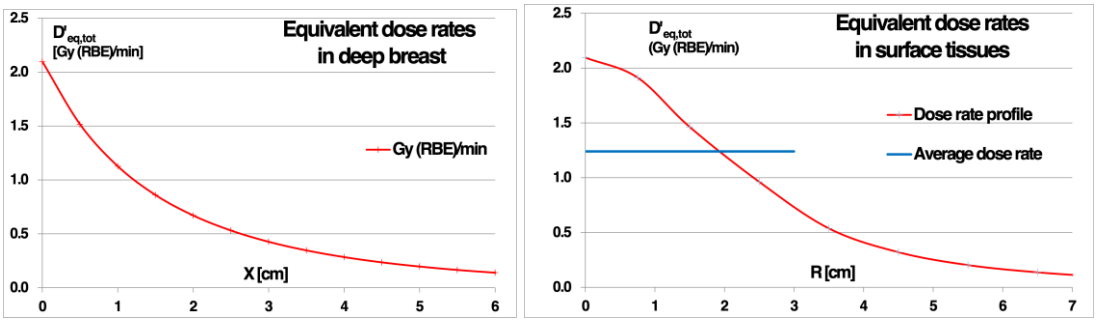


**Fig. 4:** MCNP results about the equivalent dose rate profiles in depth (left) and along superficial tissue (right, with the average value in the 6 cm irradiation window).

**Methodology**

In parallel with the experimental characterisation of the first CNG prototype, a new DD-CNG design is currently under development. As shown in the illustrative sketch in the left frame of Fig. 5, the new design envisages an applicator pipe to be adopted in IORT treatments (instead of the irradiation window used for materials characterisation measurements; Fig. 2). The IORT applicators, via hard-docking, can be inserted close to - or in contact with - the tumour bed inside the surgical cavity. The potential performances of this configuration - suitable to be installed in an OR dedicated to nIORT® treatments - were evaluated by MCNP simulations foreseeing the CNG equipped by an IORT applicator (almost transparent for neutrons) with a 6 cm diameter and about 2 cm length.

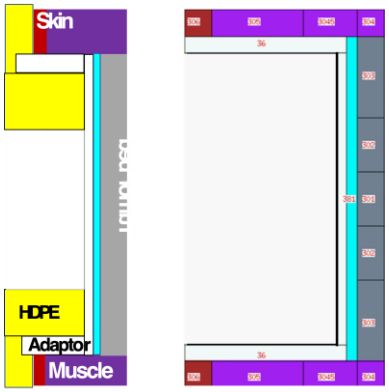


**Fig. 5**: Illustrative sketch of the IORT applicator with surrounding tissues in the surgical cavity (left), Zoom on the MCNP model of the IORT applicator and surrounding tumour bed (grey), muscle (purple) and skin (dark red) tissues
(right: red numbers refer to the MCNP cells numbering).

The right frame of Fig. 5 shows a zoom on the MCNP model of the IORT applicator and the surrounding "open wound" biological tissues in the surgical cavity. The 5 mm thick cellular tissue around the applicator represent the surface of the surgical cavity. The numbers in red colour refer to the cells numbering adopted in the MCNP model for the cylindrical IORT applicator (cell 36), the tumour bed in front of it (grey cells 301, 302, 303), the "healthy" muscle (purple cells 304, 3045, 305) and skin (dark red cell 306) tissues on its lateral side. Obviously, the tumour bed margins are not so "well-defined" as in the MCNP model but, in any case, the flux and dose rate levels were accurately calculated and monitored in the tissues all around the IORT applicator. A thin air gap (light blue cell 381) was foreseen between the applicator end-cap and the tumour bed, that is to consider an average distance between them for the "not uniform" contact for the tissue irregularities.
The Monte Carlo simulations were not restricted to neutrons (*i.e.*, the primary ones from the Ti target and the secondary ones coming from the scattering with the CNG walls and into the biological tissues), but they also include the photons: i.e., gammas created by neutrons interaction with matter. The physical dose rates (Gy/min) into biological tissues due to neutrons ($D'_{f,n}$) and gammas ($D'_{f,g}$) were calculated by MCNP by simulating the nIORT® treatment of the breast cancer. The total equivalent dose rate values ($D'_{eq,tot}$ in Gy (RBE)/min; see Fig. 4) in breast, muscle and skin tissues were obtained by:

$$D'_{eq,tot} = D'_{eq,\gamma} + \int w_n(E) D'_{f,n}(E) dE \quad (1)$$

[Gy (RBE)/min]

where:

- "$w_n(E)$" is the radiation weighting factor for neutrons (@16 at 2.45 MeV);
- the radiation weighting factors for photons is one (i.e., $D'_{eq,\gamma} \equiv D'_{f,\gamma}$);
- the level of the photon flux at the irradiation window and in the superficial tumour bed tissues is about twenty time lower than the neutron one. Because of higher flux (@20x), LET (@5x) and RBE (@16x), the neutrons contribution to the total dose rate results three order of magnitude higher than the photons one.

**Results**

In the view of possible clinical applications, the CNG performances for nIORT® treatments were evaluated by:

- adopting the clinical endpoints defined in the standard IORT techniques [33];
- deducing the correspondent Treatment Time (TT) needed to administer such dose targets in a single session from the equivalent dose rate results of the MCNP simulations.

Referring to the IORT technique with electrons (IOERT), in dependence of the tumour bed (and patient) conditions two dose targets are conventionally adopted: the so-called Boost IORT and Radical IORT regimes foreseeing endpoints of about 10-12 and 20 Gy (RBE), respectively. [34]
Table 1 reports the dose rate levels delivered in the surface tissues of the surgical cavity, calculated by MCNP envisaging a 6 cm diameter applicator for the nIORT® treatment of the breast cancer (see Fig. 5). As a Monte Carlo code, MCNP is affected by the statistical noise of the results due to its stochastic nature. For easiness, the uncertainty of the dose rate results was not indicated: their relative standard deviation is however lower than ~1%. Referring to the MCNP cells numbering in Fig. 5, the dose rates were evaluated in all the 0.5 cm thick tissue cells surrounding the IORT applicator: they represent the highest dose administered in the tumour bed and surrounding muscle and skin (healthy) tissues in the surgical cavity. The 0.5 cm thickness was chosen to represent the superficial tissues of the surgical cavity in which the overwhelming part of the dose is released (see dose profile in the left frame of Fig. 4).
For the tumour bed, the peak, middle and minimum values were calculated. Actually, the middle value of 2.2 Gy(RBE)/min refers to cell 303 located at an intermediate radius (~1.5 cm) of the IORT applicator, while the average value in the whole tumour bed volume -modelled with 0.5 cm thick (grey) cells

for a total radius of 3 cm - results @1.5 Gy(RBE)/min.
For the muscle tissue on the lateral side of the applicator, the maximum dose rate occurs in cell 305 close to skin (cell 306). These two "healthy" tissues receive almost the same dose rate (0.65 Gy(RBE)/min), that is about 4 times lower than the one administered at the centre of the tumour bed. The average value in the whole muscle volume (0.5 cm thick cells on the @2 cm lateral side of the applicator) results about 0.6 Gy(RBE)/min.

**Table 1**: Total equivalent dose rate values in the biological tissues of the surgical cavity (MCNP results for the treatment of the breast cancer with a 6 cm diameter IORT applicator).

| **Total dose Rate** | **Peak in Tumour bed** | **Middle in Tumour bed** | **Minimum in Tumour bed** | **Peak in "healthy" Muscle** | **Peak in "healthy" Skin** |
|---|---|---|---|---|---|
| **Gy (RBE)/min** | 2.70 | 2.20 | 1.15 | 0.66 | 0.65 |
| **Cell** | 301 | 302 | 303 | 305 | 306 |

Table 2 illustrates the CNG irradiation performances for different dose regimes by foreseeing clinical end-points ranging from 10 up to 75 Gy (RBE). The Boost and Radical IORT regimes are contemplated by assuming 10 and 20 Gy (RBE) for the peak and average dose targets in the tumour bed: it results evident that the TT is limited to about 4÷9 minutes, depending on the endpoint chosen (10÷20 Gy (RBE)). It should be noted that the average dose value in the tumour bed refers to the "middle" cell 302, while the maximum value refers to cell 301 where the dose rate reaches up to 2.7 Gy (RBE)/min (see Table 1).

**Table 2**: CNG irradiation performances for nIORT® treatments in Boost (10 Gy(RBE)), Radical (20 Gy (RBE)) and Ultra-Radical (> 20 Gy (RBE)) regimes (with a 6 cm diameter IORT applicator).

| **Dose Target Gy (RBE)** | **TT min** | **Peak in Tumour** | **Average in Tumour** | **Minimum in Tumour** | **Peak in Muscle** | **Peak in Skin** |
|---|---|---|---|---|---|---|
| **10 as peak** | **3.7** | **10.0** | 8.2 | 4.3 | 2.4 | 2.4 |
| **10 as average** | **4.6** | 12.3 | **10.0** | 5.2 | 3.0 | 2.9 |
| **20 as peak** | **7.4** | **20.0** | 16.3 | 8.5 | 4.9 | 4.8 |
| **20 as average** | **9.1** | 24.5 | **20.0** | 10.5 | 6.0 | 5.9 |
| **50 as peak** | **18.5** | **50.0** | 40.7 | 21.3 | 12.2 | 12.0 |
| **75 as peak** | **27.8** | **75.0** | 61.1 | 31.9 | 18.3 | 18.1 |

Actually, by envisaging 20 Gy (RBE) as average dose target in the tumour bed, the peak dose delivered in its centre reaches up to 24.5 Gy (RBE). This case could be also classified as belonging to the so-called Ultra-Radical IORT regime. Thanks to the high dose rates, even higher dose targets could be administered in a limited TT, as sometimes it should be required in the most severe cases of pancreatic ductal adenocarcinoma (PDAC) cancer and the glioblastoma multiforme (GBM) brain tumour. As reported in the last two rows in Table 2, the 50÷75 Gy (RBE) target range could be administered by a single irradiation spot of about 19÷28 min only. It can be noticed that, in the BNCT field, the 12.6 Gy (RBE) limit is usually assumed as peak dose for the healthy tissues. [35] In the DD-CNG with the IORT applicator of 6 cm diameter, this limit results exceeded in the "healthy" muscle and skin tissues around the applicator when the peak dose in the centre of the tumour bed exceeds 50 Gy(RBE)/min.
The picture on the left side of Fig. 6 shows the 2D neutron flux spatial distribution nearby the IORT applicator. As expected, the flux peak in the surgical cavity (~$10^8$ $cm^{-2}$ $s^{-1}$) is obtained at tissues surface at the centre of the tumour bed in correspondence of the IORT applicator symmetry axis. The plot

on the right side of Fig. 6 shows the total equivalent dose rate profiles in depth in breast and muscle tissues: the dose rates were sampled with 0.5 cm thick cells (with 1 cm radius) along the symmetry axis of the cylindrical applicator. As in Fig. 4 it is evident that, going in depth, the dose level drops by one half in the first centimetre of tissue and decreases by a factor @4 at 3 cm. Therefore, by comparing the left and right picture of Fig. 6, it can be seen that the neutrons diffuse into tissues but, because of their high LET and RBE, the overwhelming part of the dose is released at their surface. The deep tissues are still irradiated by the thermal and epithermal tails of the neutron flux having decisively lower LET and RBE values, and hence significantly less effective in cell damaging.

It can be finally remarked that the results reported in Fig. 6, Tables 1 and 2 refer to:

- the breast cancer case. However, these figures of merit could be generalised to the treatment of other solid tumours which, in some cases, develop radioresistance to low-LET IR radiotherapy. Of course, for more accurate results, the topography of the tissues into (and around) the surgical cavity has to be properly modelled;
- the nIORT® applicator with 6 cm diameter. Different diameters could be evaluated by obtaining slightly different figures of merit. For instance, with larger diameters the ratio between average and peak doses in the tumour bed will decrease, as well as the ratio between the peak doses in healthy and tumour bed tissues. To be however noticed that, since the applicator is rigid, larger diameters would be challenging to be used in difficult achievable body parts, such as pelvis and narrow cavities.

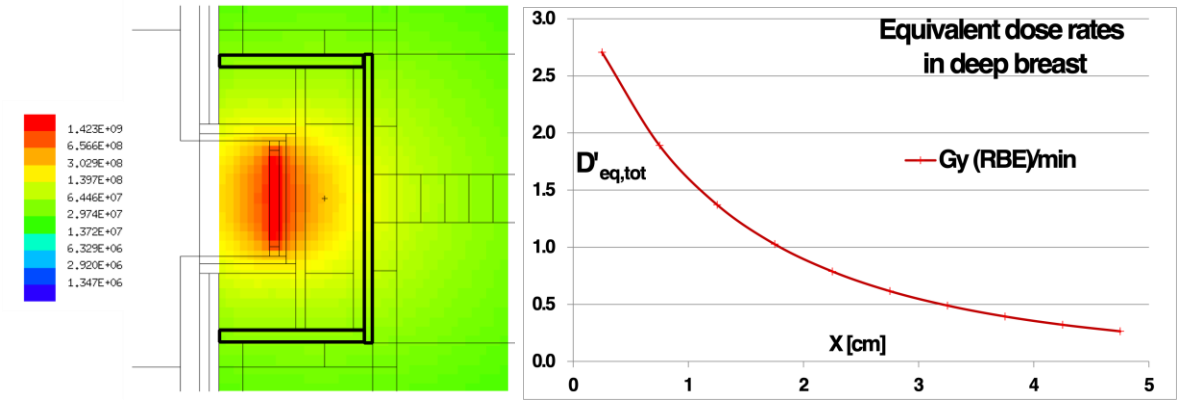


**Fig. 6:** 2D neutron flux spatial distribution nearby the IORT applicator (marked by a thicker black line; left) and equivalent dose rate profiles in tissues depth (right).

**Discussion**

As mentioned, the nIORT® could satisfy all five R's criteria of radiotherapy. [22] The reoxygenation effects (needed to fix DNA damage) are enhanced by the IORT modality in which the OER is less affected by the tumour cell hypoxia in case of neutron IR. [15] For the same reason, the reassortment - that in the EBRT is due to the rapid cells proliferation in which the heterogeneity in cell cycle kinetics re-distributes (reassorts) cancer cells over the cycle between daily fractioned irradiations - and the repopulation (of residual cancer cells in the tumour microenvironment) do not play a role in a single-dose nIORT® delivered during surgery.

For what concerns the cells repair, it had been widely understood that high-LET IR is rather effective in cancer cells killing through DNA DSBs, as well as DNA DSB clustering, but, at the same time, this lethal effect is counterbalanced by DSB-repair pathways that can act on DNA ends, such as the homologous recombination (HR), single strand annealing (SSA), nonhomologous end joining (NHEJ) and theta-mediated end joining (TMEJ). Which pathway is used for the repair of DSBs follows from the enzymes that act at the DNA end. [13,36,37] Nevertheless, some pre-clinical studies suggest that DNA ends of DNA damage induced by high-LET IR are more prone to end processing compared to DNA ends of DNA damage induced by low-LET IR. [12] While the number of lethal DNA lesions for cancer cells (as DSBs and more complex lesions) is proportional to dose, the repair system of cancer cells becomes saturated at higher dose levels. Published evidences support the hypothesis that saturation of the repair system leads to increasing genomic instability that may contribute to inactivate tumour cells as the dose per fraction is increased beyond the dose range normally studied *in vitro*.

[38,39] Furthermore, some trials indicated that the DNA of cancer cells repairs more slowly and produces also more DNA breaks (single and double) than normal cells, also because various proteins involved in cell death and DNA damage mechanisms decrease the radioresistance of the fast-doubling cancer cells, while increase the radioresistance of slow doubling normal cells. [40]

For what concerns the cells radiosensitivity, even whether the underpinning radio-biological mechanisms are not still fully understood, there exists an increasing amount of data at the biochemical level concerning the IR effects due to accelerator-produced charged particles (as protons and heavy ions), but few data concerning the effects due to high-LET beams of fast neutrons. Nevertheless, the neutron radiobiology experiments clearly identified a higher cell kill per unit dose and an accompanying reduction in oxygen dependency. [12] The neutron ionisations in living tissues are mainly caused by recoil protons of energy proportional to the neutron energy with the maximum RBE (@20) at about 1 MeV [9] comparable with the protons RBE in the Bragg peak.

The difficulties and limitations of the EBRT with fast neutrons [17,18,19] are mostly avoided by the IORT modality. The MCNP analyses demonstrated that the DD-CNG can deliver equivalent dose rates ~2 Gy (RBE)/min thanks to the high neutron flux (@$10^8$ $cm^{-2}$ $s^{-1}$), high-LET (~ 40 KeV/ µm as average) and high RBE (@16) of the 2.45 MeV neutrons (vs. 1 for electrons and X-rays). Therefore, the clinical endpoints foreseen in the Boost, Radical and, for the most severe pathologies, in Ultra-Radical regimes could be administered in very limited TTs (see Table 2).

The n-IORT® could be employed in different dose regimes with some significant additional advantages in comparison with the standard IORT techniques. By relying on the peculiar features of the fast neutron beam and the correspondent flux/dose rate spatial distributions in tissues (see Figs. 3, 4 and 6 referring to the breast cancer case, but generalizable to the treatment of many other solid cancers), the possible benefits in the view of potential nIORT® treatments can be summarised at it follows.

(1) The highest dose level is released at tissues surface in the centre of the tumour bed, where the high flux of 2.45 MeV neutrons is very effective in cells killing by inducing direct DSBs and their oxidative damages. Thanks to the high radiosensitivity and the limitation of the cancer cells repair, the neutron IR with high LET and RBE could also induce the killing of the motile Cancer Stem Cells (CSCs) or Metastatic CSC (MCSCs) infiltrating the tumour bed, while other IR as X-rays and electrons do not have enough LET/RBE to lead to necrosis and apoptosis and, in some cases, induce these cells to develop radioresistance.

(2) The limited range of penetration of fast neutrons, for which the overwhelming part of the dose is released at the surface tissues of the surgical cavity. Indeed, going in depth, the dose level is halved in the first centimetre of tissue and decreases by a factor @4 at 3 cm, sparing the neighbouring OARs from harmful radiations.

(3) The almost "*spherically symmetric*" field of the neutron beam (see Figs. 3 and 6), in which the neutrons diffusion into the tissues acts as a sort of IR "foam" filling the surgical cavity. The isotropic fast-neutron IR should allow to induce necrosis and apoptosis of the QCCs within the topography irregularities of the tumour bed and, maybe, also overcome their radioresistance (responsible of multistage cancer progression and cancer metastasis too). Therefore, the neutron beam features should allow maximizing LTC and reducing the probability of local recurrences.

(4) The almost isotropic distribution of the nIORT® IR does not require an accurate beam focusing and, in case of large target areas, it does not require the knowledge of the status of the surgical margins and lymph nodes before the treatment as in the case of standard IORT.

(5) There exists preclinical evidence that the so-called Radiation Induced Bystander Effect (RIBE) is not induced by neutrons. [41] Therefore, a lower risk for Radiation Induced Secondary Malignancies (RISMs) should occur.

(6) The monoenergetic neutron spectrum of the nIORT® would set the OER to about the plateau of @1.45 [15] because of the radiobiology effect of the neutrons in biological tissues: therefore, nIORT® is less affected by the tumour hypoxic microenvironment.

(7) The potential appearance of the Radiation Induced Abscopal Effect (RIAE) on distant non-irradiated cells due to the adaptive immune system [42,43], that is also favoured by the epithermal and thermal tails of the neutron flux spreading out around the tumour bed.

(8) It should be intriguing to investigate in preclinical tests if neutrons of 2.45 MeV energy could inhibit the Epithelial-Mesenchymal Transitions (EMTs) in solid cancers. If verified, this potential feature would be fundamental since EMTs represent a crucial process endowing the cancer cells with invasive and metastatic properties, as well as radioresistance. [44,45,46]

(9) In the nIORT®, the tumour-specific immune responses should be enhanced by the RBE of

2.45 MeV fast neutrons (@16), significantly higher than the unitary value for electrons and low-KeV X-rays used in the standard IORT. If this hypothesis turns out to be validated in pre-clinical tests, then the nIORT® could become a promising clinical practice to be used in the most sever solid cancer cases such as as advanced stage tumors, GBM and PDAC tumours.

**Conclusions**

The potential advantages of n-IORT® treatments to be administered to oncological patients with different solid cancer pathologies were described. The high flux (~$10^8$ $cm^{-2}$ $s^{-1}$), high LET (~ 40 keV/mm as average) and high RBE (@16) of the 2.45 MeV neutrons beam produced by the 100 kV-10 mA DD CNG should allow to deliver high dose targets in very short (one-shot) treatment times: e.g., 10 to 20 Gy (RBE) in 4 to 9 minutes. Furthermore:

- the almost spatial-isotropic diffusion of neutrons allows to irradiate the surrounding QCCs in the surgical cavity by reducing the chances of local recurrences;
- the overwhelming part of the dose is released in tissues surface, sparing the neighbouring OARs from harmful radiations;
- higher clinical endpoints, e.g., up to 75 Gy (RBE) as it could be required in the most severe PDAC and GBM cases, can be administered in one-shot irradiation of less than half an hour.

Of course, the potential advantages here discussed will have to be carefully investigated and verified by *in vitro* and *in vivo* [47,48] preclinical tests, sufficiently comprehensive to identify strengths and weaknesses of the nIORT® treatment, especially versus the traditional IORT.

Electronic brachytherapy systems with low KeV X-rays (@1) is currently pursued on equine patients in several hospitals worldwide for convenient and effective treatments. nIORT® has a much higher (@16) RBE than the above mentioned practice, therefore nIORT® application might be much more successful for the equine treatments [49,50].

The design of the 100 kV-10mA DD-CNG equipped a typical IORT applicator and its shielding structure is currently under development. These components will be integrated into one unit specifically designed for its potential utilization in ORs dedicated to nIORT® treatments. The compact size and light-weight (~120 kg) would make possible its remote handling by a robotic arm. The experimental evidence in working with DD-CNGs indicates that the apparatus will be capable to administer about 2500 hours of nIORT®, without producing any environmental and safety concerns.

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**Ethical Statement**

The authors are accountable for all aspects of the work and contributed equally to this research.

**Author contributions**

Martellini M, Sarotto M., Leung K and Gherardi G contributed equally to this work.

**Conflicts of Interest**

Authors Martellini M, Sarotto M, Leung K and Gherardi G declare that they have no conflicts of interest.

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