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Potential Applications of the Compact Fast-Neutron Generator for the Adjuvant Treatment of Solid Tumours with the Intra-Operative Radiotherapy (nIORT®) Technique: Simulation and Dosimetry Analyses with the MCNP Code

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Abstract: The potentiality of the intraoperative radiotherapy (IORT) with fast neutrons as an adjuvant treatment for severe solid cancers has been investigated in a 5-year research program. The therapeutic dose is administered by a single irradiation directly within the surgical cavity after surgical resection by means of a compact neutron generator (CNG) with the so-called neutron-IORT technique patented as nIORT®. Two CNG prototypes – exploiting the deuterium–deuterium fusion reaction to produce neutrons of 2.45 MeV energy - are currently undergoing experimental characterisation with the main objectives of demonstrating: the therapeutic effectiveness of fast neutrons, having a relative biological effectiveness (RBE) ≈ 3÷4 times greater than that of standard RT treatments with X-rays and electrons, and low sensitivity to hypoxia; the feasibility of installing the CNG - surrounded by ~1 m cube shield - in a hospital operating room dedicated to nIORT® treatments, without posing safety and environmental concerns. In parallel, several dosimetry analyses have been conducted using the MCNP Monte Carlo code by a detailed modelling of the CNG equipped with cylindrical and hemispherical nIORT® applicators positioned within brain and breast surgical cavities, respectively. Thanks to the high neutron flux (~10^8 cm^{-2} s^{-1}) and leveraging on the high RBE of fast neutrons, the MCNP simulations indicate that dose targets of ~10 Gy(RBE) could be administered in ~10÷20 minutes only. Moreover, the diffuse neutron beam may enable: (i) the treatment of large and topographically irregular tumour beds, which remain challenging targets for the focused beams employed in standard RT and IORT techniques; (ii) the irradiation of the tumour bed margins - typically infiltrated by quiescent cancer cells and locale recurrences - thereby potentially enhancing the local tumour control; (iii) a limited damage and adverse effects to the nearest organs at risk, due to the limited penetration of neutrons over few centimetres in the biological tissues; (iv) to integrate the nIORT® adjuvant treatment for radioresistant tumours with local recurrences in a multimodal approach integrating surgery, chemotherapy and/or immunotherapy. In memory of Marina Gherardi, Marika de Feo and Gianluca Costamagna

INTRODUCTION

The common radiotherapy (RT) techniques for the treatment of solid cancers with photon X-rays - combined with sophisticated imaging technologies - have reached a significant development and nowadays represent a standard in clinical applications. Despite several

successful outcomes, the treatment efficacy is intrinsically limited by their low linear energy transfer (LET) in biological tissues (~1÷2 keV/μm in standard X-rays RT [1]), that often causes insufficient DNA damage to destroy the tumour cells [2]. The cells damage is more dispersed and uniform with low-LET radiation (as X- or γ-rays) and more discrete, clustered, and heterogeneously scattered along the beam tracks with high-LET particles leading to necrosis of the cancer cells. Thus, hadron-based therapies exploiting protons and carbon-ions have been investigated and shown promising results in achieving better local tumour control (LTC). Proton therapy, for instance, allows precise dose delivery with minimal exposure to surrounding healthy tissues, making it an attractive option for complex tumours [3]. Carbon ion therapy combines the advantages of proton therapy with higher LET and biological effectiveness, potentially offering even greater benefits [4].

Among high-LET particles, fast neutrons represent a possible option for the treatment of radioresistant tumours with high risk of local recurrence. Some remarkable clinical outcomes were achieved in the 1970s and 1980s with the fast neutron therapy (FNT) for many lethal pathologies, such as head and neck cancers, bone and soft tissue sarcomas, advanced prostate cancer, breast and bladder cancers ([5], [6], [7], [8], [9], [10]). The high-LET neutrons are very efficient against cancer cells also for their minor sensitivity to hypoxia, characterising some of the previous pathologies - as well as e.g., the lung mammalian carcinomas and the pancreatic ductal adenocarcinoma (PDAC) - in which cancer cells are very resistant to conventional RT techniques with low-LET particles, typically inducing DNA single-strand breaks, often efficiently repaired by the organism. Otherwise, the efficacy of the fast neutrons is not influenced by the oxygen enhancement ratio (OER [11]), typically low in the hypoxic tumour microenvironments (TMEs): the high-LET particles damage directly the DNA of tumour cells with fewer but larger double-strand and multiple breaks per unit dose (more difficult to repair) and indirectly by concurrent secondary effects leading to the cancer cells' death through a major release of reactive oxygen (and nitrogen) species and free radicals.

Despite some remarkable clinical outcomes, the results obtained were controversial and the development of the FNT was left behind mainly because of: (i) the complex and costly equipment required for producing neutron beams, e.g., nuclear reactors and accelerators; (ii) the damage to normal tissues and organs surrounding the treated tumour, with possible long-term toxicity effects due to the high-LET neutrons; (iii) the biological mechanisms of neutron interactions with the tissues not fully understood, with some discrepancies in the dose-response relationships making difficult to define precise dosimetry parameters and, then, to establish standardized clinical protocols ([12], [13]).

Besides the historical data collected in the 1980s-1990s, modelling studies are currently ongoing to evaluate the actual neutron biological effectiveness for DNA damaging [14]. Some recent clinical investigations have been conducted e.g., for the glioblastoma multiforme brain tumour (GBM), also characterised by hypoxia and slow growing invalidating the efficacy of X-rays RT and/or chemotherapy treatments [15]. The efficacy of standard techniques against this lethal pathology results to be limited also because X-rays enhances the GBM cells motility [16]. Contrarily, high-LET radiation - as carbon ions and □ particles - does not induce GBM cells migration / invasion and reduce significantly their survival by increasing the treatment efficacy [17]. Similar clinical studies on GBM were carried out also in the past with fast neutrons: although the FNT did not improve overall survival, the examination of the histological material indicated a considerably greater antitumor effect

than after treatments with standard X-rays [18]. Thus, even if the historical clinical results were controversial and many oncologists in the past were uncertain whether the high LET of fast neutrons truly translated into better outcomes compared to conventional RT:

- the biological mechanisms of their interactions with the tissues were not fully understood and more recent studies indicate encouraging results in comparison with low-LET RT treatments;
- as discussed in this article, there are some margins to exploit the potentiality of high-LET neutrons for their peculiar physical features, that could overcome some difficulties encountered with the standard RT techniques against the most lethal cancers.

To compare RT techniques utilising different irradiation particles, the biological response triggered by exposure is commonly expressed through the relative biological effectiveness (RBE). This parameter represents the ratio of doses required by two different radiation types (e.g., neutrons and photons) to induce the same biological effect, using specific reference photons with a unitary RBE value [19]. The RBE value is influenced by many physical and biological factors, such as the particle mass and energy, the type of tissue, the dose level and its fractionation. About the dose levels, it was found that the RBE of fast neutrons of different energy resulted to be higher when low dose values are administrated (~1÷5 Gy) and decreases with higher dose levels ([20], [21], [22], [23]).

Diverse nuclear reactions can be exploited to produce fast neutrons within distinct energy ranges, as fissions, deuterium-deuterium (D-D) and deuterium-tritium (D-T) fusion reactions, (p, n) reactions by protons accelerated against lithium or beryllium targets, etc. While the neutron production is usually accomplished with nuclear reactors, cyclotrons and linear accelerators requiring big and costly installations, this research study is based on the utilisation of a compact neutron generator (CNG) exploiting the D-D fusion reaction to produce neutrons of 2.45 MeV energy [24]. Certainly, the possibility to adopt a compact source represents a sensible reduction of the costs and a fundamental advantage in the view of the possible installation in a hospital operating room (OR). The 2.45 MeV energy represents an optimal trade-off between the required efficacy of fast neutrons against cancer cells - with a LET ~30÷50 keV/mm [25] - and the shielding required to respect safety and radiation protection limits in a hospital, that e.g., it would be decisively more challenging with the 14-MeV-energy neutrons produced by D-T reactions. Regarding the RBE value at ~2.5 MeV energy and with dose targets ~5÷10 Gy, in some clinical studies it was measured in the 3÷5 range for tumour cells and limited to about 2.5 in normal tissues (e.g., [22],[23]).

After a brief description of the CNG design and its cube shield in borated polyethylene (PE) (see chapter 2), this article summarizes some outcomes of the 5-year research activity carried out by the Theranosti Centre S.r.l. (TC) company in collaboration with the Italian National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA). Two CNG prototypes were purchased by TC and nowadays are installed in a new equipped ENEA laboratory for their experimental characterization [26]. In parallel, several simulations with the Monte Carlo N-particle (MCNP [27]) code were carried out to evaluate the main dosimetry parameter that could be potentially obtained with an innovative intra-operative radiotherapy (IORT) with fast neutrons: the neutron-IORT technique patented by TC at the European level as nIORT® [28]. Being the intra-operative

modality a one-shot session, a target dose level ~10 Gy is usually required [29] and, as indicated by the MCNP simulations of the nIORT® treatment applied to the brain and breast surgical cavities, this clinical end-point could be reached in a single session of ~10÷20 minutes (see chapter 3).

Despite the prospective outcome data are still limited [30], the IORT advantages - due to the instant prevention of tumour regrowth, optimised dose-sparing of adjacent healthy tissue and immediate completion of metastases treatment - are nowadays considered comparable with the long-term outcomes of the external-beam RT, or even superior when applied in the optimal setting e.g., for brain malignancies [31]. With advancements in delivery techniques, in some cases the IORT treatment after the maximal (or partial) surgical resection of the tumoral mass is becoming a standard with related guideline recommendations, e.g., for the treatment of the GBM tumour with X-rays ([31], [32], [33]) or electrons [34]. Differently from the external-beam RT with fractioned sessions performed some days or weeks after surgery (on the skin upon the "closed wound"), the dose target is administered in a one-shot irradiation directly within the surgical cavity, allowing the zeroing of the time to initiation and limiting the repopulation of residual cancer cells in the TME. Relying on these operational advantages deriving from the IORT approach, some difficulties and limitations of the FNT treatments made in the past could be overcome by the nIORT® modality with a one-shot treatment, that should reduce the damage to the organs surrounding the tumour bed and could limit also the long-term toxicity. It must be taken into consideration that the excessive toxicity historically associated with neutrons in the past was partly due to an inadequate radiobiological understanding: conversely, recent clinical studies have demonstrated better clinical outcomes using low-dose neutrons compared to photons of standard RT techniques [35].

Besides the MCNP simulation of the nIORT® treatment of the breast and brain tumours (see chapter 3), for the sake of comparison the dose profiles obtained by MCNP in the superficial and deep tissues of the brain surgical cavity (after craniotomy) were compared with the ones deriving from conventional IORT techniques. Two IORT techniques recently investigated for the treatment of patients affected by GBM brain tumours based on:

1. low-energy X-rays at 50 keV [32];
2. high-energy electrons at 1 MeV [34].

were considered and simulated also with the MCNP code. Besides the effectiveness of the high-LET and high-RBE neutrons in treating radioresistant cancers, the diffuse beam should allow to treat tumour beds with significant extension and topographic irregularities, that remain a therapeutic challenge with existing technologies foreseeing a focused-beam and/or a beam with a limited target area. The impossibility to confine the radiation beam in a limited target could appear as a limitation but, as highlighted by the dosimetry analyses, the diffuse neutron beam exhibits complementary features respect to these standard IORT (and more generally RT) techniques for what concerns both:

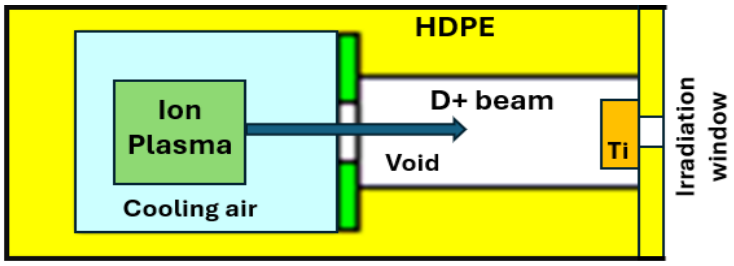
- the dose profiles in the superficial tissues, by irradiating the tumour beds and their margin potentially filled by quiescent cancer cells (QCCs);
- the dose gradient in tissues depth (see chapter 4).

It is worth to notice that this research study deals only with the radiological aspects associated with the IORT treatments and does not concern with any other relevant clinical issues related to the specific cancer pathology. Consequently, even if this article analyses the simulated nIORT® treatment of brain and breast cancers, owing to the flexibility of the CNG apparatus it is possible to argue that the same technique could be potentially applied to other solid tumours in different organs and parts of the body.

It is worth noting that this study focuses exclusively on the radiological aspects of IORT and does not address the broader clinical issues associated with the management of specific cancer types. Accordingly, although this work investigates simulated nIORT® treatments for brain and breast cancers, the irradiation with the CNG could be potentially extended to other solid tumours in different organs and anatomical sites. Furthermore, as the conventional RT and IORT treatments, the nIORT® technique could be inserted in a multimodal approach integrating surgery, chemotherapy (e.g., Stupp protocol for GBM [36]) and/or immunotherapy [37], that may represent a decisive step in improving survival and quality of life for patients (see chapter 5).

THE CNG DESIGN AND PROTOTYPES

The CNG design principle is shown in the conceptual scheme in the top part of Figure 1. The D+ ions are created in a RF plasma chamber and accelerated against a titanium target cooled by air. The titanium lattice occludes and traps neutral D atoms and, when the accelerated-incident D+ ions overcome the Coulomb barrier and collide with them, the fusion reaction is triggered by generating fast neutrons of 2.45 MeV energy close to the irradiation window. Besides the source compactness, the main advantageous design features of the CNG are summarised in the bottom part of Figure 1.



NO	Nuclear proliferation
	High level waste
	Separate box for DC voltage

YES	Portable
	Switch On/Off
	Limited cost

Figure 1: Conceptual design and main features of the D+ ion-based CNG.

The research program carried out by TC and ENEA in collaboration with the Berkion Technology LLC company (BT, USA) led to the CNG design patent [38] and the fabrication of the first two prototypes shown in Figure 2. The CNG prototypes were built in the BT laboratories, purchased by TC and are nowadays installed in a new equipped laboratory in

the ENEA research centre in Brasimone (BO) for their experimental characterization e.g., CNG beam measurements by means of an anthropomorphic phantom equipped with neutron and gamma detectors.

The second prototype shown in the right part of Figure 2 was conceived for in vitro tests on commercial cancer cells and foresees some technological advancements - such as operation reliability, safety, and radiation protection aspects - that should make the apparatus suitable to be installed in an OR dedicated to nIORT® treatments without posing concerns for patients and operators. As indicated by the preliminary analyses carried out in the ENEA laboratories, this objective should be fulfilled by enclosing the "kernel" of the CNG in a borated PE cube of ~1 m side, with an external layer in lead to shield secondary ▫-rays. A picture of the CNG kernel is shown in the left part of Figure 3: it mainly consists in the cylindrical accelerator column made of high density PE (HDPE, see Figure 1) with ~15 cm diameter and ~30 cm length.

Figure 2: Two CNG prototypes adopted for radiation protection (left) and radiobiological measurements.

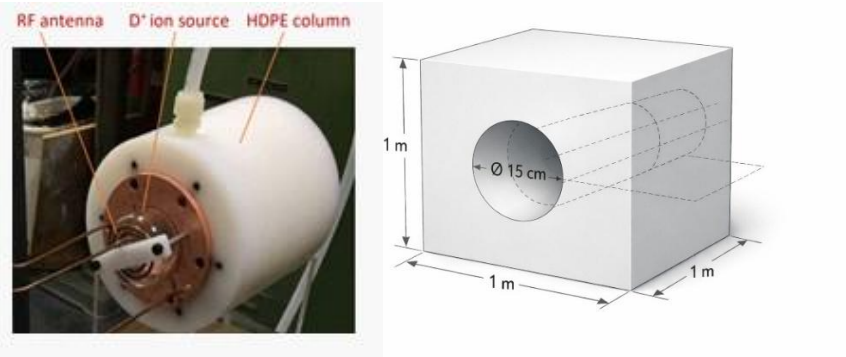


Figure 3: Picture of the CNG accelerator column (left) and conceptual scheme of its cube shield in borated PE (right).

The right part of Figure 3 shows a conceptual scheme of the cube shielding in borated PE. The CNG kernel will be inserted in the ~15-cm-diameter hole in the central-front part of the shield oriented toward the patient. The rear and lateral sections of the borated polyethylene (PE) cube provide effective shielding against neutron leakage into the surrounding OR environment, thereby facilitating compliance with IAEA radiation protection requirements for hospital staff working in supervised areas and for the general public [39]: as a net result, the thickness of the concrete walls separating controlled and supervised areas could be significantly reduced.

MONTE CARLO SIMULATIONS OF nIORT® TREATMENTS FOR BRAIN AND BREAST CANCERS

Physical and Weighted Dose Calculation Methodology

The CNG performances for potential nIORT® treatments were evaluated by means of the Monte Carlo code MCNP ver. 6.1 [27] coupled with the most up to date ENDF/B-VIII.0 nuclear data [40]. Operating the CNG prototypes at 100 kV-10 mA DC, a neutron yield of 3.3 10^9 s^{-1} is generated in 2-cm-diameter cylindrical volume at the centre of the titanium target impinged by the D+ ion beam: simulating the angular distribution of the emitted neutrons (slightly forward-oriented [24]) the neutron flux results ~108 cm^{-2} s^{-1} at the irradiation window (see Figure 1). Differently from the CNG design features of Figure 1, as foreseen in the IORT modality the irradiation window is replaced by an applicator pipe to be inserted in the surgical cavity (see chapter 3.2). Starting from the flux levels in the irradiated tissues, the absorbed (physical) dose is calculated in MCNP by means of tabulated kerma (kinetic energy released to matter) factors available in nuclear data [40].

The uncertainty of the MCNP results reported in this article is not indicated: however, their relative standard deviation is lower-equal than ~1% for all calculated flux and dose rate values.

As mentioned, the RBE value depends on several factors and, for neutrons with ~2.5 MeV energy and dose target ~5÷10 Gy, it was measured in the 3.5-5 range in cancer cells - e.g., for the melanoma tumour - and limited to about 2.5 in normal tissues [23]. To obtain the "weighted" (i.e., clinical-equivalent) dose values – usually expressed in Gy(RBE) and derived from the absorbed ones in Gy - the RBE value was assumed constant and equal to 3.5 for all tissues of the brain and breast surgical cavities, potentially filled with QCCs and local metastases.

The absorbed dose distributions (Gy) in the superficial tissues of the surgical cavity around the nIORT® applicator and in tissues depth were estimated with MCNP (see chapter 3.3), that simulates the interaction of neutrons in the tissues and of the secondary photons generated by these interactions. Starting from the absorbed dose rates due to neutrons (D'f,n) and secondary prompt gammas ($D'_{f,n}$) expressed in Gy per minute (Gy/min), the weighted dose rate (D'_{eq}) - expressed in Gy (RBE)/min - can be obtained by the following equation:

$$D'_{eq} = RBE_{\gamma} \cdot D'_{f,\gamma} + RBE_n \cdot D'_{f,n} \text{ [Gy (RBE)/min]} \quad (1)$$

where:

- the RBE value of secondary photons in biological tissues (RBE_{γ}) was assumed unitary (as for X-ray and electron particles in chapter 4);
- the RBE value of fast neutrons in biological tissues (RBE_n) was assumed 3.5 for all the tissues of the surgical cavities. Thus, the weighed dose rate refers to the cancer cells, while in normal tissue (RBE ≅2.5) the administered dose should be reduced by about 30% obtaining a sort of binary irradiation with the partial selectivity of tumour cells. In the boron neutron capture therapy, a higher selectivity is obtained by means of injected ^{10}B carriers, but a thermal spectrum is needed.

The weighed dose rate profiles were calculated starting from the absorbed ones in the biological tissues due to neutrons and photons - calculated directly by MCNP - and then multiplied with the corresponding RBE values as in equation (1). The neutrons' contribution in superficial tissues results ~700 times greater than the contribution of secondary prompt gammas because of the higher neutron flux (≅20x photon flux), LET and RBE values.

Referring to the clinical end point defined by standard clinical protocols, the treatment time (TT) needed to administer the aimed dose target ($D_{eq,T}$) can be easily retrieved by:

$$TT = D_{eq,T} \,/\, D'_{eq} \ [min] \qquad (2)$$

The spatial distributions of the dose rates in the surgical cavities and in tissues depth were evaluated in small MCNP cells (~1 cm^3) to estimate the maximum value administered in the superficial tissues at the centre of the tumour bed - usually corresponding to the D_{eq},T clinical end point – as well as the lower values in the surrounding tumour bed margins and normal tissues.

Currently, there is no experimental validation of the MCNP dose calculations in biological tissues. While long-term clinical confirmation may eventually become available, the measurements to be performed at ENEA using the CNG prototype and an anthropomorphic phantom equipped with detectors and sample vials will provide the first experimental evidence to assess the reliability of the simulated dose distributions.

MCNP Model of Cylindrical and Hemispherical nIORT® Applicators

In view of potential nIORT® applications the irradiation window of the CNG (see Figure 1) is replaced by an applicator pipe to be inserted in the surgical cavity. The nIORT® applicator is incapsulated in a thin lucite ($C_5O_2H_8$) cap, that protrudes from the cube shield of few centimetres (see Figure 3) and, via hard-docking, can be inserted close to - or in contact with - the tumour bed in the surgical cavity. Usually, in standard IORT treatments with X-rays or electrons, the applicators are cylindrical or spherical [41] in shape. In our scoping studies ([42], [43], [44], [45]), cylindrical and hemispherical applicators were respectively considered to simulate the brain and breast nIORT® irradiation, to treat e.g., brain gliomas or mammalian carcinomas. Figure 4 shows a zoom of the MCNP model of these two applicators - both 4 cm in diameter – in which:

- the hemispherical shape (left frame) was assumed for the breast irradiation to obtain an almost uniform (*i.e.*, iso-level) dose distribution on the superficial tissues of the surgical cavity;
- the cylindrical shape (right frame) was assumed for brain tumours irradiation with craniotomy, in which the maximum dose is administered frontally around the central symmetry axis of the applicator (positioned in correspondence of the tumour bed's centre) and reduced dose levels are administered in the surrounding brain, skull and skin tissues.

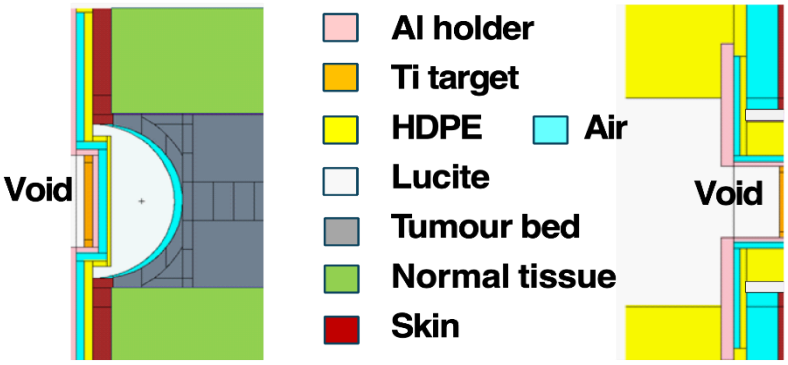


Figure 4: Zoom of the MCNP model of the 4-cm-diameter hemispherical (left) and cylindrical (right) nIORT® applicators inserted in breast and brain surgical cavity, respectively (the void parts represent the internals of the CNG accelerator column in HDPE).

In both cases, a thin air gap was introduced between the applicator endcap and the tumour bed (see light blue cells in Figure 4), that is to consider an average distance between them for simulating the tissue irregularities. Certainly, the tumour bed extension is not so well-delimited as in the MCNP model (with a net separation between the brain/breast tumour bed and normal tissues) but, in any case, the flux and dose rate levels were calculated in small volumes (*i.e.*, MCNP cells) modelling the tissues all around the nIORT® applicators.

Main Results: Dose Rate Profiles and Treatment Times

The main figures of merit for the potential nIORT® treatments with the two applicator shapes were calculated by MCNP starting from the 2.45-MeV-energy neutrons emitted from the titanium target. The left part of Figure 5 shows the 2D map of the neutron flux obtained with the hemispherical shape: the diffuse beam leads to an almost iso-level dose distribution in the superficial tissues of the whole breast surgical cavity. This feature can be clearly seen in the right part of Figure 6 where the 1D dose rate profiles - obtained with both applicators in the superficial tissues - are compared. As sketched in the left part of Figure 6, the "R" horizontal axis in the dose rates graph represents:

- in the cylindrical case, the radius of the tumour bed in correspondence of the applicator end-cap until 2 cm, while bigger R values refer to the skull and skin tissue on its lateral side;
- in the hemispherical case, the distance from the centre of the tumour bed of the tissues around the hemispherical lucite cap.

As clearly shown in the right part of Figure 6, while an almost iso-level dose distribution is obtained with hemispherical shape, by adopting the cylindrical nIORT® applicator:

- higher dose rate values are obtained, mainly for the shorter distance between the titanium target source and the tumour bed (see Figure 4);

- the maximum dose levels are administered at the centre of the tumour bed and, aiming LTC, lower dose values are administered in the tumour bed margins and surrounding skull and skin normal tissues;
- a relative dose peak is administered in skin (see last value), higher than the pre-last one in skull since, as can be seen in the MCNP model in Figure 4, the skin cells result to be closer to the titanium target than the skull ones.

Since IORT, and more generally RT, must balance delivering a sufficient dose to eradicate the tumour against limiting the real risk for adverse responses in normal tissues, the possible choice between the two applicator shapes for the IORT® treatment - supplying different spatial dose distributions in the surgical cavity - could represent an advantageous option. As expected, very similar behaviours were found for the flux and dose profiles in brain and breast depth: the right part of Figure 5 shows the weighted dose rate profile in the tumour bed and brain tissues below it. The dose rate values were sampled with cylindrical cells (1 cm in radius and 0.25÷0.5 cm in thickness) along the "X" symmetry axis of the applicator: the dose level drops rapidly decreasing by a factor 2 at ≅1 cm depth and by a factor 5 at ≅2.5 cm. Thus, the overwhelming part of the dose is administered in the superficial tissues and until 1 cm depth, while it strongly decreases in depth avoiding excessive irradiation of normal tissues and closest organs at risk (OARs). As mentioned in chapter 3.1, the uncertainty of dose rate values in Figures 5 and 6 is below 1% at the 1□ level, while 2D flux map (in the left part of Figure 5) was obtained with the mesh tally option in MCNP, mainly adopted for visualization purposes and characterised by a slightly higher uncertainty.

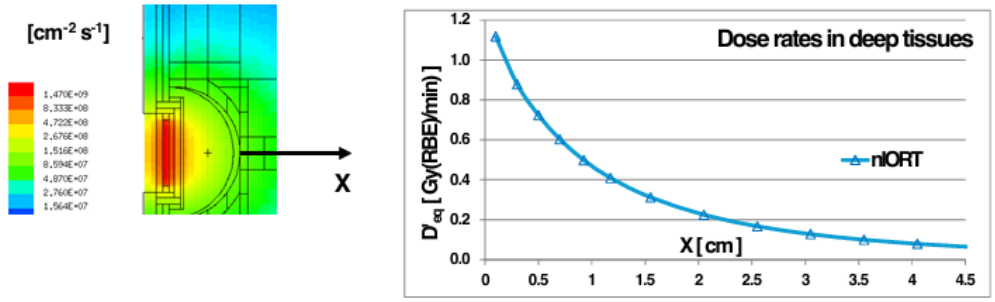


Figure 5: MCNP results: 2D map of flux levels in breast surgical cavity with the hemispherical nIORT® applicator (left); 1D dose rate profiles in brain depth with the cylindrical nIORT® applicator (right).

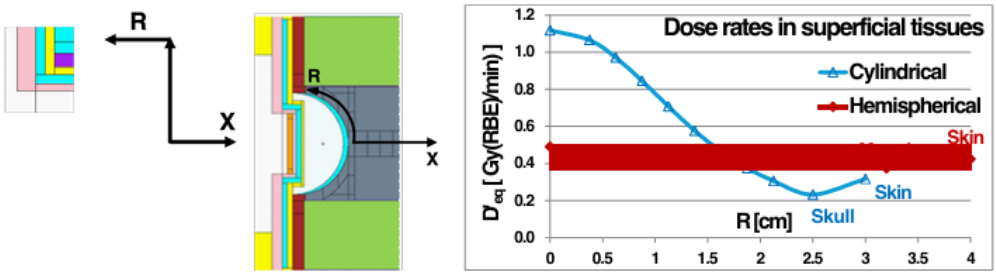


Figure 6: MCNP results: 1D dose rate profiles in the superficial tissues of brain and breast surgical cavities, obtained along R axes in the cylindrical and hemispherical nIORT® applicators.

Table 1 reports the weighted dose rates (Gy(RBE)/min) administered by the 4-cm-diameter cylindrical and hemispherical nIORT® applicators in the superficial tissues of the brain and breast surgical cavities: they were calculated by means of volume tallies in MCNP considering surface cells of 2÷3 millimetres thickness (see Figure 4). The maximum, average and minimum values in the tumour bed - as well as the maximum ones in the surrounding normal tissues (i.e., skin and skull) are reported: the dose rate values are negligibly influenced by the composition and density of the biological tissues and, as clearly shown in Figure 6, primarily depend on the applicator shape chosen.

Table 1: Weighted dose rates in the superficial tissues of the brain and breast surgical cavity with cylindrical and hemispherical nIORT® applicators (4 cm in diameter): maximum, average and minimum values in the tumour bed and peak values in the normal tissues [Gy(RBE)/min].

nIORT® applicator shape	Organ	Tumour bed			Peak in normal tissue	
		Max	Average	Min	Skin	Skull
Cylindrical	Brain	1.09	0.53	0.33	0.35	0.25
Hemispherical	Breast	0.47	0.42	0.41	0.36	

From Figure 6 and the results in Table 1, it appears evident that:

- the cylindrical applicator supplies an almost *front focused* dose distribution with:
    - a maximum dose rate of ≅1.1 Gy(RBE)/min administered in the tumour bed's centre;
    - limited dose rates in the tissue on the lateral side of the applicator (*e.g.*, ≅32% of the peak in the closest head skin);
- the hemispherical applicator supplies an almost (uniform) *iso-level* dose distribution beam with:
    1. a maximum dose rate of ≅0.5 Gy(RBE)/min administered in the tumour bed's centre;
    2. dose rate values at the margins of the tumour bed and in surrounding skin reaching the ≅87% and ≅77% of the maximum, respectively.

In dependence of the tumour bed (and patient) conditions, different dose targets are usually adopted. By considering the boost regime with a clinical end-point of 10 Gy(RBE) [29], the potential performances of the CNG-nIORT® apparatus for a one-shot session can be retrieved by equation (2): treatment times of 21 / 9 minutes are obtained with the hemispherical / cylindrical applicator, respectively. Finally, it is important to notice that:

- the dosimetry parameters obtained for the brain and breast cancers irradiation can be generalized to the nIORT® treatment of other solid tumours in different organs and parts of the body;
- the performances of the apparatus are evaluated in the nIORT® irradiation conditions, but the CNG could be also adopted (as in standard FNT) for external-beam RT treatments of superficial tumours, e.g., skin melanomas [23].

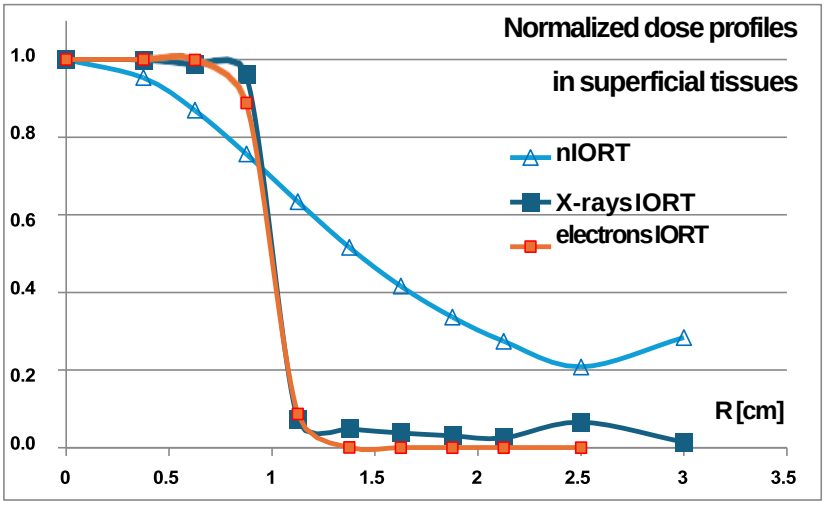
COMPARISON BETWEEN nIORT® AND STANDARD IORT TREATMENTS

Keeping the MCNP model of the cylindrical nIORT® applicator of 4 cm in diameter inserted in the brain surgical cavity (see right frame of Figure 4), the MCNP code was also adopted to simulate the IORT irradiation with standard IORT techniques adopting 50-keV-energy X-rays [32] and 1-MeV-energy electrons [34]. In both cases, a focused beam of 2-cm-diameter was simulated, a unitary RBE value was assumed and the source particles were generated directly on the external (circular) surface of the applicator endcap, thus crossing only a thin air gap - simulating tissues' irregularities (see chapter 3.2) - before reaching the tumour bed.

Since the photon radiation has a significant power of penetration, coherently the MCNP simulations were not restricted to the primary X-rays and considered secondary electrons, by including their contribute to the dose rate results. Otherwise, in the simulations with the impinging 1 MeV electrons, no secondary particles were foreseen since in low-atomic-number media (such as water or tissues) electrons lose energy predominantly through ionization and excitation events (i.e., inelastic collisions with atomic electrons). The MCNP code simulates properly these phenomena: indeed, as the beam of electrons travels the tissues, the energy is continually degraded until they reach thermal energies and are captured by the surrounding atoms.

The left and right parts of Figure 7 compare the normalized dose profiles obtained with the cylindrical IORT applicator by fast neutrons, X-rays and electrons in the superficial tissues of the brain surgical cavity and in brain depth, respectively. It appears evident that:

- in superficial tissues (left part), the focused beams of X-rays and electrons irradiate only the central part of the tumour bed in a 1-cm-radius circular area (*i.e.*, beam radius), while the diffuse neutron beam irradiates - with decreasing dose levels around the central peak - the whole tissue area in front of the 2-cm-radius applicator endcap, the skull and skin tissues on its lateral side (see also Figure 6);
- in brain depth (right part), fast neutrons result less penetrating than X-rays for the higher LET (*e.g.*, the neutron / X-ray dose drops by a factor 20 / 2 in 5 cm depth, respectively) and more penetrating than electrons, whose dose profile drops to zero after ≅0.5 cm in brain tissues.



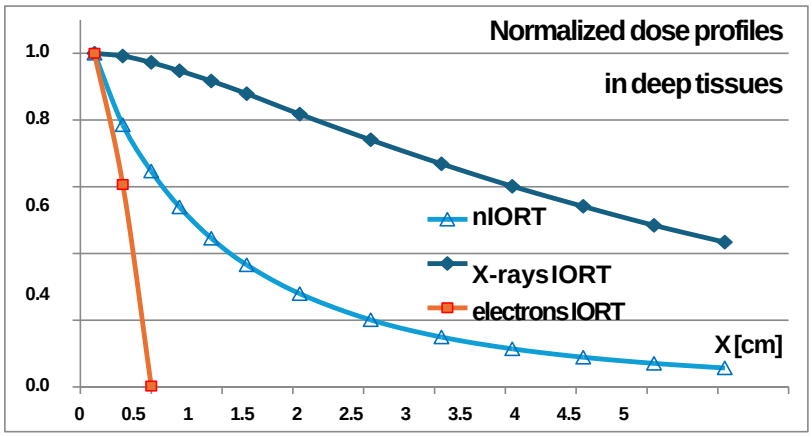


Figure 7: MCNP results with 4-cm-diameter cylindrical IORT applicator: normalized dose profiles in the superficial tissues of the brain surgical cavity (left) and in brain depth (right) with nIORT®, X-rays IORT and electrons IORT techniques.

The dose profiles of Figure 7 are reported as normalized to remark the complementary features of the nIORT® potential treatments respect to the standard IORT techniques, for the peculiar spatial dose distributions in both superficial and deep tissues. The diffuse neutron beam permits to irradiate larger areas of the surgical cavity (with potential local recurrences), not allowed by standard techniques with focused beams; the dose profile in tissues depth is not steep as the electrons one and not penetrating as the X-rays one. Regarding the comparison of beam power among different IORT techniques, the dose rate of approximately 1 Gy(RBE)/min delivered by the CNG to superficial tissues (using the cylindrical applicator) can be achieved by X-ray and electron IORT systems with source yields approximately 300 times higher and 4 times lower, respectively.

CONCLUDING DISCUSSION AND REMARKS

Advances in RT delivery techniques have led to the emergence of the IORT as a viable option for adjuvant treatments following the tumour resection, by eliminating delay in time to initiation after surgery, reducing the treatment toxicity and avoiding the complexity of target delineation in the post-operative period. The leading idea of this research study is the IORT treatment of sever solid cancers with fast neutrons by the so called nIORT® technique, relying on a very compact source: the CNG exploiting the D-D fusion rection producing 2.45-MeV-energy neutrons and guaranteed for ~2500 hours of safe operation. Two CNG prototypes are currently being experimentally characterized at the ENEA laboratories by means of radiation protection and radiobiological measurements. As indicated by preliminary studies, the CNG could be safely shielded by a PE cube of ~1 m side and potentially installed in a hospital OR dedicated to nIORT® treatments without posing safety and radiological concerns for patients and healthcare personnel. The MCNP code was adopted to model the CNG equipped with cylindrical and hemispherical nIORT® applicators to be inserted in brain and breast surgical cavities: the results of the simulations indicated that the CNG-nIORT® system could administer dose targets of ~10 Gy(RBE) in a one-shot treatment of ~10 and ~20 minutes, respectively. The high-flux, high-LET and high-RBE of fast neutrons should induce necrosis or programmed cell death in tumour cells even in hypoxic conditions.

The MCNP dosimetry analyses refer to the nIORT® irradiation of breast and brain tumours (*e.g.*, as the malignant carcinoma and GBM) by adopting 4-cm-diameter applicators, but the flexibility of the apparatus should allow to generalize these results to other cancer pathologies in different organs and parts of the body. The dose profiles obtained show peculiar features in both superficial and deep tissues of the surgical cavities, that could be advantageously exploited in balancing the need for an effective LTC.

Regarding the dose profile in superficial tissues, the diffuse beam produced by the CNG-nIORT® apparatus does not permit to confine the neutron radiation in a limited target area. This aspect could appear as a limitation but, at the same time, it could be particularly suitable for the surgical cavities with large and topographically irregular tumour beds, that are still a therapeutic challenge for standard RT and IORT treatments exploiting focused beams. Furthermore, the two nIORT® applicator shapes supply different spatial dose distributions (in superficial tissues):

- an almost *iso-level* distribution is obtained with the hemispherical applicator in the whole breast surgical cavity;
- a *front focused* distribution is obtained with the cylindrical applicator, in which the dose peak is released in the centre of the brain tumour bed and lower values are administered in surrounding tissues potentially filled with local recurrences.

In dependence of the tumour bed extension and conditions, the possible choice between the two applicator shapes - supplying different spatial dose distributions in the surgical cavity - could represent an advantageous option for the aimed LTC. About the dose profile in tissues depth, the nIORT® show complementary features respect to conventional RT and IORT treatments: the profile obtained with fast neutrons is not as steep as the electrons' one and, at the same time, not penetrating as the X-rays's one. In any case, the overwhelming part of the dose is administered in the superficial tissues until ≅1 cm depth, by limiting the radiation damage to the neighbouring OARs.

Certainly, differently from the X-rays and electrons IORT (and more generally RT) nowadays accessible with established protocol, a lot of research and clinical studies are necessary to demonstrate the nIORT® efficacy against radioresistant pathologies, as the brain and breast tumours here considered. At the same time, since historical clinical studies with fast neutrons revealed successful outcomes against severe tumours (as neck cancers, soft tissue sarcomas, prostate and bladder cancers), these promising results could be "replicated" and maybe enhanced by the IORT modality.

As the standard RT and IORT techniques - the nIORT® could be inserted in a multimodal approach integrating surgery, chemotherapy and/or immunotherapy. Preclinical data suggest a biologic interaction between RT and immunotherapy with several clinical studies corroborating these findings, e.g., for the treatment of malignant skin melanomas [46] and brain neuroblastomas, by exploiting the combination of high-LET particles with some drug molecules as the APR-246 [47]. It was also found that the treatment with APR-246 - a reactivating compound of the p53 agent exhibiting accelerated senescence and significant rates of apoptosis in response to RT applied to PDAC and colorectal cancers - enhances the sensitivity of cancer cells to high-LET □ particles, leading to reduced tumour growth and increased rates of its eradication [48]. The RT is also able to induce antitumor immunity not only in the irradiated primary tumour but also at unirradiated distant sites of

metastases [49]: thus, the diffuse beam of the nIORT® - irradiating also the tumour bed margins potentially filles by QCCs with lower dose levels - could lead to even more advantageous outcomes than those indicated by early-phase clinical trials combining standard RT and immunotherapy.

One of the main objective of this research study was devoted to the nIORT® treatment of brain tumours as the lethal GBM, since it was proven that the standard IORT technique – eventually combined with novel targeted immunotherapeutic approaches with immune checkpoint inhibitors and other targeted therapies - provides a promising alternative to adjuvant external beam RT, by enabling superior organ-at-risk preservation, reduction of in-hospital times and timely admission to subsequent systemic chemotherapy treatments [50]. Furthermore, as nowadays quality of life at the time of tumour recurrence is higher than in the past in a great number of patients, second surgery is increasingly considered a valid option also for the GBM [51]. The surgical rejection could be combined with the nIORT® treatment, in which the diffuse beam should particularly efficient against the (re-)grown local recurrences, frequently observed within 2÷3 cm from the initial GBM lesion and representing the major cause for clinical deterioration and patients' death.

List of abbreviations

CNG	Compact Neutron Generator
D-D	Deuterium-Deuterium
D-T	Deuterium-Tritium
FNT	Fast Neutron Therapy
GBM	GlioBlastoma Multiforme
HDPE	High Density PolyEthylene
IORT	Intra-Operative Radiation Therapy
LET	Linear Energy Transfer
LTC	Local Tumour Control
MCNP	Monte Carlo N-Particle (code)
nIORT®	Neutron IORT
OAR	Organ At Risk
OER	Oxygen Enhancement Ratio
OR	Operating Room
PDAC	Pancreatic Ductal AdenoCarcinoma
PE	PolyEthylene
QCC	Quiescent Cancer Cell
RBE	Relative Biologic Effectiveness
RT	Radiation Therapy

TME Tumour MicroEnvironment

TMZ TeMoZolomide

Symbols

D'_f Absorbed dose rate [Gy min^{-1}]

D'_{eq} Weighted dose rate [Gy (RBE) min^{-1}]

$D_{eq,T}$ Weighted dose target (or clinical end-point) [Gy (RBE)]

TT Treatment time

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