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Secondary Radiation in Ion Therapy and Theranostics: A Review

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Ion therapy has emerged as one of the preferred treatment procedures in some selective indication of cancer. The actual dose delivered to the target volume may differ from the planned dose due to wrong positioning of the patient and organ movement during beam delivery. On the other hand, some healthy tissues outside the planned volume may be exposed to radiation dose. It is necessary to determine the primary particle range and the actual exposed volume during irradiation. Many proposed techniques use secondary radiation for the purpose. The secondary radiation consists mainly of neutrons, charged fragments, annihilation photons, among others, and prompt gammas. These are produced through nuclear interaction of the primary beam with the beam line and the patient's body tissue. Besides its usefulness in characterizing the primary beam, the secondary radiation contributes to the risk of exposure of different tissues. Secondary radiation has significant contribution in theranostics, a comparatively new branch of medicine, which combines diagnosis and therapy. Many authors have made detailed study of the dose delivered to the patient by the secondary radiation and its effects. They have also studied the correlation of secondary charged particles with the beam range and the delivered dose. While these studies have been carried out in great detail in the case of proton and carbon therapy, there are fewer analyses for theranostics. In the present review, a brief account of the studies carried out so far on secondary radiation in ion therapy, its effect, and the role of nuclear reactions is given.

Keywords: theranostics, neutrons, prompt gamma, charged particle, ion therapy, secondary radiation

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INTRODUCTION

In the growing incidence of malignant diseases, ion therapy has emerged as a preferred choice of treatment in the case of some selective indications [1–4]. During the passage of charged particles through the patient's body, electronic interactions contribute to the major part of energy deposition, while nuclear reactions lead to the production of neutrons, gamma rays, and secondary charged particles (SCPs). The energy deposition characteristics and the depth dose profile of the charged particle beams help to have high-dose conformity in the target volume in a static patient in an ideal situation. But variation in patient positioning and organ movement during treatment cause a fraction of the dose to be delivered outside the planned target volume [5, 6]. The problem can be circumvented if the actual volume of dose distribution can be dynamically imaged. This is achieved to some extent in image-guided radiotherapy (IGRT) [7] whence the target volume is imaged during treatment. Proposed techniques also use the SCPs to determine the primary particle range and the delivered dose during patient irradiation. Theranostics is an improved version of therapy [8] which combines treatment with simultaneous imaging of the region of interest. This is gradually emerging as a targeted and efficient mode of treatment.

Secondary particle dose is clinically important because neutrons can result in radiation dose to a distant organ, while heavy fragments can locally deposit a high dose. Both neutrons and SCPs have high radiobiological effectiveness (RBE). So measurement of yield, flux, and dose of the secondary particles is crucial for assessing the probability of radiogenic cancer [9] at a later stage. As the prospect of new beams is being studied, benefits as well as risks from secondary radiation need to be investigated thoroughly.

This is a review work of the studies carried out by different authors on secondary radiation in ion therapy and in theranostics, its effect, and the role of nuclear reaction. Yield and dose distribution of charged particles and neutrons from ion-induced reaction in tissue, their correlation with the primary ion range, and contribution to the total dose will be discussed.

SECONDARY RADIATION IN ION BEAM THERAPY

In radiotherapy, exposure to the healthy tissues is lesser in the case of charged particle therapy (CPT) compared to that in the case of photon therapy due to the characteristic of interaction and energy deposition of charged particles in matter. In charged particle therapy, the energy of the carbon beam is in the range of ~80–430 MeV/u, while the proton energy is in a lower range. For these moderately relativistic particles, the energy loss takes place through Coulomb and nuclear interaction. Nuclear interaction results in the loss of beam intensity contributing to both longitudinal and lateral dose profile [10, 11]. Multiple elastic scattering on the target nuclei contributes to the lateral profile and results in a broadening of the beam. Inelastic scattering with the atomic electrons contributes to the longitudinal profile. In CPT, nuclear reaction of the primary beam takes place both with the beam line components and within the patient's body. This leads to the production of neutrons, protons, heavier nuclear fragments, and deexcitation gamma rays. The nuclear fragments may consist of positron emitters and other radioactive isotopes. The former will give rise to annihilation gamma rays. Annihilation gammas, prompt gamma rays, neutrons, and the SCPs may help in dynamic imaging of the dose distribution. In proton therapy, nuclear fragmentation results in target fragments which consist mainly of secondary protons and neutrons. In heavy ion therapy, both target and projectile fragments are produced. Both the projectile and the target fragments contribute to the increase in the RBE. The projectile fragments enhance the lateral spread of the beam and add to the dose in the tail region of the Bragg peak. The dose distribution due to SCPs, neutrons, and gammas needs to be determined accurately to assess the biological effect.

Proton and carbon beams are most widely investigated for ion beam therapy. New beams like ^{4}He, ^{16}O are being studied to assess their possible advantages in ion beam therapy. ^{4}He ions might turn out to be a good choice, as projectile fragmentation and neutron production are expected to be lower than in the case of ^{12}C beams while having good localization of the energy deposition [12, 13]. For ^{16}O, fragmentation is higher and *in vitro* studies had also provided a slightly larger RBE value [14, 15] compared to ^{12}C, but carbon beam has a higher impact on cell survival. However, in all the cases, actual volume which is exposed to primary and secondary radiation strongly depends on patient positioning and on anatomical variation of the target organ during treatment [5, 6]. This necessitates determination of the actual volume where the dose is released. The SCPs produced in the nuclear reaction, particularly the secondary protons, can be well used as a tool for imaging in CPT [16, 17].

Secondary Charged Particles

Experimental Studies

Cross-section, total yield, fluence distribution of SCPs, and their contribution to the total dose had been investigated by several authors [12–39]. Target fragmentation for proton induced reactions in tissue equivalent targets like water, PMMA, C, and CH_2 was studied in the energy range of 40–250 MeV [19–21]. A study on 250 MeV proton on water showed that around 40% of the primary particles were lost in inelastic collision on their way up to the Bragg peak. The LET value and the range of the target fragments produced in these interactions were between 983 keV/μm down to 14 keV/μm and 2.3–68.9 μm, respectively. This resulted in the alteration of the fixed RBE of 1.1 used for proton therapy beam and contributed to the dose beyond the planned target volume [21]. For an unmodulated 160 MeV proton beam and a target volume of $3 \times 3 \times 3\,cm^3$, the dose from secondary protons to the proximal part of the Bragg peak was ~10% [19]. The dose contribution from d, t, α, and ^{3}He was less than 0.1% of the total dose proximal to the Bragg peak.

Nuclear fragmentation in carbon-induced reaction in tissue equivalent targets at 80–430 MeV/u was measured in many works [22–39] to determine the actual dose and range. The total [22–26] and partial (ΔZ = 1, 2, 3 for the formation of B, Be, and Li, respectively) [22, 23] charge-changing cross-sections in the interaction of ^{12}C in water were determined between 110 and 600 MeV/u. The total SCP production cross-section was found to decrease as the beam energy increased in the work of Golovchenko et al. [22], while no such trend was observed in [23]. Production of B was measured to be ~2.3–3 times that for Be [22, 23]. Charge-changing cross-sections for ^{16}O beam incident on thick targets of water and carbon were also measured [24].

Kinetic energy of the secondary protons emitted in the interaction of therapeutic ^{12}C beams extended beyond the primary beam energy per nucleon [27, 28]. At 80 MeV/u beam energy, yield of protons with E_p = 83 MeV was found to be $\sim 2.7 \times 10^{-4}$ sr^{-1} [27]. At 200 MeV/u, energy of emitted protons extended beyond twice the beam energy per nucleon [28] and the yield of protons with E_p = 350 MeV was $\sim 5 \times 10^{-5}$ ion^{-1} sr^{-1} MeV^{-1}.

Production of secondary fragments for carbon-induced reactions at 95 MeV/u [25, 29] and for 200–400 MeV/u was measured and discussed in several works [28, 30–39]. Among all the fragments, yield of H and He was highest [28, 30, 31] and was similar or higher than the primary ions near the end of range. The yield fell off rapidly as the fragment charge increased [28]. Beyond the Bragg peak, light fragments H, He, Li, Be, and B had significant contribution. At 400 MeV/u beam energy, the

fragments penetrated few centimeters after the Bragg peak [30, 33]. These fragments would thus contribute to the delocalization of dose.

The angular distribution of the fragments was forward peaked for all fragments, was broad for light fragments, and became narrower as nuclear charge increased [30, 33]. At 219 and 280 MeV/u beam energy, protons had a broad angular range (up to 10°), but the primaries were confined within a narrow cone [34]. At 200 MeV/u, fragments heavier than He were confined in a cone of about 5° width. This suggested that the angular distribution was governed by the fragmentation process and not affected much by Coulomb scattering. The yield of secondary fragments integrated between 0 and 10° was highest for protons and lowest for Be [28]. At 400 MeV/u beam energy, the FWHM for H, He, and B was 10, 5.3, and 3°, respectively [30]. Higher FWHM was measured in the works of G. D. Lellis et al. [32] and K. Gunzert-Marx et al. [28].

The contribution of the secondary fragments to the dose equivalent within the Bragg peak was ~20%, 13%, and less than ~8% of the total dose for 157 MeV proton, 145 MeV/u ^{4}He, and 219–383 MeV/u 12C beams, respectively [12, 13, 34]. Beyond the Bragg peak, the total dose was contributed by the secondary fragments only. This dose in the tail region might affect the healthy tissue [30, 33].

At therapeutic energies, the target fragmentation rate was ~3.62 times higher for carbon ion compared to that for proton beam [12]. But the absorbed dose and dose equivalent due to the secondary target fragments (STFs) were 0.22% and 4%, respectively, of the primary ion dose for ^{12}C, compared to 1.2% and 20%, respectively, for proton beam. This was explained from the fact that though the yield of STFs increased with Z/β (β = velocity of primary ion), the number of primary ions required to produce a given dose decreased as Z^2 [40]. These results excluded the dose contribution due to secondary neutrons produced in the reaction. Among the secondary fragments, the highest dose was contributed by the light fragments H and He [30, 31] in the tail region behind the Bragg peak. They caused delocalization of the dose, followed by Li.

Besides proton and carbon, performance of ions like ^{4}He, ^{16}O, and ^{20}Ne in heavy ion therapy was investigated in several works [14, 15, 41–49]. The total number of secondary protons produced by 220 MeV ^{12}C beam in PMMA target at 90° was $(4.49 \pm 0.13 \pm 0.59) \times 10^{-3}$ sr^{-1} which was ~4.5 times that produced by 125 MeV ^{4}He (having the same range as 220 MeV ^{12}C in PMMA) [41, 42]. Production of ^{2}H and ^{3}H was ~5%–10% and ~1%–2%, respectively, of the total production of ^{1}H+^{2}H+^{3}H. For 125 MeV/u ^{4}He projectile, the energy of the emitted ^{1}H extended beyond 240 MeV at 5° [42]. Significant production of β^{+} was also reported for ^{4}He ion on PMMA target [43]. Secondary proton fluence from 300 MeV/u ^{16}O induced reaction on PMMA target was measured to be $(74.18 \pm 0.40 \pm 13.02) \times 10^{-3}$ sr^{-1} at 60° and was ~6.5 times lower at 90° [14]. At 210 MeV/u ^{16}O beam energy, these values were ~3.3–3.6 times lower. For the interaction of 670 MeV/u Ne beam in water, oxygen, and fluorine had the highest yield among the target fragments with $Z \geq 3$, while at 400 MeV/u in PMMA target, oxygen had the highest yield followed by carbon and nitrogen [31]. Boron was found to have significant contribution at both the energies [31, 46]. In studying the efficacy of intensity modulated composite particle therapy (IMPACT), influence of the secondary particles on LET distribution was assessed [47, 48].

In CPT, annihilation gammas from positron emitters produced in nuclear fragmentation can be used for imaging during therapy. In measuring the mean range of different stable beams in water, polyethylene, and PMMA, from activity distribution using annihilation gammas, highest amount of information was obtained in the case of ^{16}O beam to determine the mean range of the beam accurately. Thus, ^{16}O turned out to be the optimum among stable beams for monitoring the range from annihilation gammas [50]. In proton therapy, annihilation gammas could be used to achieve a dose-volume guided radiotherapy system with a 2 mm spatial resolution [51, 52]. The profile of the prompt gamma rays produced in the interaction of the ion beam was also used to establish a relation between the gamma ray profile and the primary ion range [53–58]. Time-of-flight (TOF) technique was used to discriminate between prompt gammas, neutrons, and neutron-induced gamma rays. With less background and higher contrast, the peak and the dose fall off position could be measured with millimetric precision for proton beams [58].

The tracks of SCPs, their flux, velocity, and spatial distribution were analyzed and reviewed for monitoring in hadron therapy [16, 17, 19, 59, 60]. The Bragg peak position could be determined from the emission profile of the SCPs with high accuracy. A linear correlation was observed between the position of the distal edge of the secondary particle tracks and the Bragg peak position [19]. Accuracy of the method depended on several factors like multiple scattering of the SCPs, inherent fluctuation in the number of emitted charged particles, and overall statistics of the measured data. Feasibility study of range monitoring of carbon ions with secondary protons was carried out using interaction vertex imaging [17, 59] which showed that single proton detection in coincidence with the incoming beam was more promising.

Simulation Studies

Simulation studies of ^{12}C interaction in water, with the Monte Carlo Geometry and Tracking 4 (GEANT4) [61] code, showed that, at a beam energy of 155 MeV/u, more than 6% of the total dose was deposited by the SCPs and gamma rays from the phantom surface to 90% of the distal edge of the Bragg peak [62]. At beam energies of 262 and 369 MeV/u, these contributions were, respectively, ~14% and 23%. As the primary dose sharply fell off beyond the Bragg peak, the secondary radiation played a much more important role. From 90% of the distal edge to 5 cm after the Bragg peak, the SCPs along with the gamma radiation contributed ~71%, 82%, and 87% to the total dose, at beam energies of 155, 262, and 369 MeV/u, respectively [62]. The major contributor to the secondary dose was ^{11}B along with H and He near and beyond the Bragg peak [63]. At 290 MeV/u, contribution from H and He ions extended more than 160 mm beyond the Bragg peak. This could affect healthy tissues outside the target volume. In the initial part of the

primary beam path, LET of the primary ^{12}C beam was ~33.6 keV/μm while those for ^{14}N, ^{15}N, and ^{16}O were almost 30 times more. However, this pattern drastically changed near and beyond the distal end of the Bragg peak. Here, ^{11,12}C, ^{16}O, and ^{13,14,15}N had almost comparable LET [62]. Experimentally measured LET distribution of SCPs, for 380 MeV/u ^{12}C beam, was compared with the GEANT simulation [64, 65]. The measured values were well reproduced by the simulation [65]. In a benchmark analysis of the reaction models available in GEANT4 simulation kit for fragmentation studies [66, 67], it was observed that the measured fragment yields were reproduced by the models within 5–35%. The QMD model with Frag option gave the best agreement. The kinetic energy and the angular distributions were best reproduced by the QMD and INCL++ models, respectively [67]. GEANT4 simulation was used to compare the mixed radiation field produced by 162, 290 MeV/u ^{12}C beam and 192, 245 MeV/u ^{16}O beam in water [68]. At these energies, the ranges of the C and O beams were the same in the target. Production of nuclear fragments was higher for ^{16}O compared to that for ^{12}C. As a result, energy deposition beyond the Bragg peak and out of the field would be more for ^{16}O.

The PHITS code [69] was used to investigate the role of nuclear fragmentation and secondary radiation in carbon therapy [70, 71]. In the PHITS simulation, the Bragg curve peaked at a depth slightly lower than that given by the measured data. This was attributed to PHITS underestimating the probability of fragment production [70]. Using the Monte Carlo particle transport code FLUKA [72], the energy distribution, range distribution, and fragment fluence were studied for H, He, Li, B, Be, C, N, and O in proton-induced reaction on water between 40 and 200 MeV [73]. The energy distribution was highly asymmetric. For Li and heavier fragments, the energy distribution extended only well below 20 MeV. Proton energy spectrum had a broad shoulder and extended above 20 MeV.

Dedes and Parodi had reviewed the status of Monte Carlo simulation of particle interaction in tissue in carbon ion therapy [74].

Neutrons

Experimental and simulation studies were carried out by several authors [28, 75–91] to investigate the fluence and dose of secondary neutrons in proton and carbon ion therapy. Production of secondary neutrons and their dose profile were found to strongly depend on the irradiation facility [75–79]. Epidemiological studies were also undertaken to analyze the significance of the neutron dose in proton therapy [92].

The incident beam energy in ion therapy is high but gradually decreases in tissue. For carbon beam from therapeutic energy down to ~12 MeV/u, the reaction cross-section is highest at the latter point [80]. At these energies, the neutron field consists of both thermal and high-energy neutrons. Thermal neutrons have isotropic distribution while the fast neutrons produced have a strong energy dependence and forward peaked angular distribution. Neutrons with energy above 20 MeV were observed only close to the beam axis [81]. The high-energy neutrons, above 20 MeV, could contribute as high as 53% of the total dose at the position of highest neutron dose. The scattered neutron distribution was highly complex and depended on the spatial characteristics of the treatment facility. This necessitated a detailed Monte Carlo simulation of the secondary neutron field [82].

In proton radiotherapy at ~172 MeV, the largest neutron dose was obtained at a distance of 115 cm from the isocenter. The finding conformed to the fact that neutrons could significantly contribute to the dose outside the target volume [83].

From a comparison of the secondary neutron ambient dose equivalent (H^*_n (10)) in passive particle radiotherapy, it was confirmed that, for passively scanned beams, H^*_n (10) was less in carbon therapy than in proton therapy [84]. This dose depended on the operational beam setting but not on the method for making a laterally uniform field. H^*_n (10) for active scanned beam was similar for carbon and proton beams. For an active scanned carbon beam, this dose was at the most 15% of passive beam [85]. The observation could be attributed to the fact that the contribution to the total neutron dose from external neutrons was much reduced by an active scanned beam compared to a passive one. For a 250 MeV passively scanned proton beam, ~35% of the total neutron dose was due to neutrons with $E_n \geq 20$ MeV [86]. The neutron dose in passive particle radiotherapy was either similar to or less than that in photon therapy [84]. Comparison of the neutron yield in CPT and in high-energy photon therapy showed that, at therapeutic energies, the yield of most effective neutrons (~1MeV with w_R of 20) was much lower in ion therapy [87]. This was one of the main advantages of ion therapy over photon therapy.

A FLUKA Monte Carlo simulation was used to model a neutron tracker developed to track secondary neutrons produced in proton therapy [93]. This would help in better modeling of secondary neutrons.

THERANOSTICS USING RADIOACTIVE ISOTOPES

Feasibility of radioactive ion beams ^{10,11}C, ^{13}N, ^{14,15}O, ^{17,18}F and ^{18,19}Ne was investigated [50, 94–96] and reviewed [97] for in-beam positron emission tomography imaging in ion therapy. In the case of ^{11}C and ^{15}O, the difference in the Bragg peak position and the position of the maximum positron emitting fragments was negligible for ideal monoenergetic beams, but this difference increased with and was strongly influenced by the energy spread of the primary beams [94]. The difference also increased with energy of the primary beam. For 250 MeV/u ^{15}O and 350 MeV/u ^{11}C beams, the measured differences of 2.0 and 4.4 mm, respectively, were well reproduced by the PHITS simulations. Of the radioactive ion beams mentioned above, ^{15}O turned out to have the best feasibility for in-beam imaging and range monitoring [50].

Another set of isotopes emerging as potential diagnostic and therapeutic nuclides are the two radioisotopes of Cu–^{62,64}Cu [95, 96, 98–107]. Cu is one of the most abundant trace transition elements in human body and plays a key role in various physiological processes. Among the five radioisotopes of Cu,

namely, ^{60,61,62,64,67}Cu, ^{62}Cu (half-life 9.67 min) decays by β+ emission and is used for diagnosis. ^{64}Cu with a half-life of 12.7 h decays by electron capture β+ and β-emission. Electron capture results in the emission of Auger electrons which can be used for therapy [100]. So ^{64}Cu is increasingly investigated for use in diagnosis as well as in therapy. In normal cells, Cu remains in the cytoplasm, but in tumor cells it migrates to the nucleus [98]. Thus, ^{64}Cu can be used for theranostics without causing toxicity to the normal cell. The effect of $^{64}CuCl_2$ on human glioblastoma multiforme cell lines was studied by Catalogna et al. [101]. This study supported the theranostic potential of $^{64}CuCl_2$ in this tumor. $^{64}CuCl_2$ could be efficiently used for PET imaging in glioblastoma multiforme [102] which supported the prospect of ^{64}Cu as a diagnostic isotope for tumors of central nervous system. $^{64}CuCl_2$ as a PET probe with PET-CT imaging could be efficiently used for determining the stage of prostate cancer in the works of Capasso et al. [103]. ^{64}Cu-ATSM radiopharmaceutical was studied for imaging of hypoxic tumor tissue. A difference between normal and hypoxic cells was revealed around 10–15 min after administration of the compound [104]. Efficacy of ^{64}Cu-labelled-DOTATATE was investigated for imaging of neuroendocrine tumors. High spatial resolution, very good image quality, and significantly improved lesion detection capability were observed compared to ^{111}In-DTPA-octreotide [105] and ^{68}Ga-DOTATOC [106], respectively. ^{64}Cu was also used to study the uptake of specific antibody in patients with metastatic or advanced primary colorectal cancer. It showed higher specificity than ^{18}F-FDG for detection of colorectal tumors [107]. Feasibility of ^{64}Cu-labelled receptor antibody was studied for early detection and image-guided surgery of pancreatic cancers and gastrointestinal cancer using PET imaging [94, 95]. It was observed that pancreatic tumors larger than 3 mm could be detected and well resected [94]. Biodistribution and radiation dosimetry studies of $^{64}CuCl_2$ showed that liver has the highest uptake of ^{64}Cu in this form [108]. This was followed by intestine and pancreas. It was suggested that therapeutic activity with ^{64}Cu (in chloride form) up to several GBq would be safely feasible for these organs.

Several nuclides mentioned above are prospective candidates for theranostic applications–there are a few bottlenecks though. For radionuclides, the specific characteristics required for good imaging are different from those required for treatment. So only a few isotopes, for instance, ^{64}Cu, offer a combination of diagnostic and therapeutic capability. Secondly, phenotype-specific radiopharmaceutical is required for theranostic applications [109]. There are difficulties also related to dosimetry and delivery of the radionuclides to the target tissue. The drug compound may not be distributed uniformly in the target volume, and dose assessment is a complex task [110]. Moreover, theranostic application requires cost-effective supply of radioisotopes, clinical and regulatory approval of radiopharmaceuticals, and trained, competent manpower.

CONCLUSION

Ion therapy has emerged as one of the preferred methods of treatment in certain indications of malignancy. Detailed studies by different authors showed that the secondary radiation produced by the beam interaction in the patient's body can be used for range correlation and fine tuning of the primary beam. ^{16}O was detected to be the optimum among stable beams for range monitoring using annihilation gammas from positron emitting fragments. Prompt gammas and SCPs could be employed for monitoring the range of the primary beam with millimetric precision. This will help to determine the actual volume where the dose is deposited. On the other hand, the secondary radiation also causes dose deposition outside the target volume. This secondary radiation includes SCPs (from projectile and target fragmentation and particle emission), neutrons, and prompt gamma radiation. Neutrons produced in the patient's body may cause exposure to some healthy tissue well outside the target volume, though the dose would be small, whereas in photon therapy a large volume of healthy tissue is exposed to significant amount of radiation dose from the primary beam itself. Thus, the probability of secondary radiogenic cancer is decreased in ion therapy compared to that in the case of photon therapy. The neutron ambient dose equivalent H^*_n (10) in passive scanning method is substantially higher than that for active scanned beam. Among all the SCPs produced, light charged particles have the highest yield and show a broad angular distribution. Heavier fragments have lower yield and are confined to a narrow cone. In theranostics using radioactive beam, new isotopes are being investigated in detail by several authors. Of these, ^{15}O has appeared as a good candidate for in-beam PET imaging and range monitoring. ^{64}Cu in its ionic form as $^{64}CuCl_2$ has good prospect as a diagnostic agent for tumors of central nervous system, hypoxic tumors, and prostate cancer. ^{64}Cu-labelled radiopharmaceuticals are effective in imaging of neuroendocrinal tumors and colorectal cancer. Annihilation gammas from the positron emitting isotope ^{64}Cu could be efficiently used for image-guided surgery in pancreatic and gastrointestinal cancer. Prospective isotopes for theranostics need to be studied in great detail in order to come up with the most effective choices.

Review Criteria

Data for this review are compiled searching the published literature including archived works with no limitation on date. Searched phrases include "ion therapy", "particle therapy", "secondary radiation", "neutrons", "theranostics", among others. References have been quoted for all the works mentioned.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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