Binary technologies of malignant tumors radiotherapy

A A Lipengolts1,2,3,4, https://orcid.org/0000-0002-5631-9016, Yu A Finogenova1,2, https://orcid.org/0000-0002-5144-1039, V A Skribitsky1,2, https://orcid.org/0000-0003-2942-7895 and E Yu Grigorieva1,2, https://orcid.org/0000-0001-7726-7991

1 N.N. Blokhin National Medical Research Center of Oncology, Kashirskoe shosse, 24, 115478, Moscow, Russian Federation
2 National Research Nuclear University “MEPhI”, Kashirskoe shosse, 31, 115409, Moscow, Russian Federation
3 A.I Burnasyan Federal Medical Biophysical Center, ul. Zhivopisnaya, 46, 123182, Moscow, Russian Federation
4 Kurnakov Institute of General and Inorganic Chemistry, Leninsky prospect, 31, 119991, Moscow, Russian Federation
lipengolts@mail.ru

Abstract. Binary radiotherapy (BRT) approach for curing malignant tumors is described in the paper. Two main modalities of BRT, i.e. Neutron Capture Therapy and Contrast Enhanced Radiotherapy are being described and compared. Physics of BRT practical implementation is discussed. Clinical efficacy of BRT in treating brain tumors and head and neck cancer as well as pharmacological challenges and achievements are being reviewed.

1. Introduction
Therapeutic application of ionizing radiation for treating tumors has a long history since X-rays and radioactivity were discovered [1]. Different types of ionizing radiation such as photons, protons, neutrons, carbon ions and many other were introduced into radiotherapy of malignant tumors. Currently radiotherapy is one of the three main methods of treating tumors along with surgery and chemotherapy. Radiotherapy provides non-invasive local damage of tumor tissues thus providing comparatively well tolerated organ-preserving efficient treatment of malignant tumors. From radiation oncologist point of view an ideal dose distribution for curing patients with radiotherapy is the distribution with the prescribed absorbed dose of radiation uniformly located within a tumor volume and with zero absorbed dose in surrounding tissues. Such simplified one-dimensional depth dose distribution is presented in figure 1.

However, if one takes a look at the depth dose profiles of the most often used in radiotherapy types of radiation (figure 2) then it can be seen that their depth dose distribution is far away from the ideal one.

Photons, electrons and neutron have nearly exponential decay with the depth and the maximum of absorbed dose is located at the surface or in close vicinity of the surface depending on the particular type of radiation and its energy. Even protons and carbon ions while having very favorable depth-dose profile for a single particle with most of the energy released in Bragg peak if considering spread out Bragg peak which is a superposition of multiple Bragg peaks of separate particles and which is necessary to cover tumor volume with necessary amount of absorbed dose then the ratio of absorbed dose values in tumor region and surrounding tissues appeared to be quite poor - just around 2.
To achieve dose distribution somehow closer to the ideal radiotherapeutic dose distribution multi field irradiation from different directions was introduced. Indeed, irradiation of a tumor from different directions with beams focused on the tumor’s volume provides necessary amount of radiation within the tumor. At the same time radiation burdening is shared with much greater volume of healthy surrounding tissue and thus in average creates less absorbed dose in them than in the tumor (figure 4).

This approach was pushed to the limit with stereotaxic radiosurgery irradiations implemented in many modern radiotherapy accelerator machines. Around several hundred directions are used to deliver prescribed therapeutic dose in a single session for a tumor not more than 1-2 cm in diameter (figure 5) [5].
Figure 3. Depth dose profiles for a single proton Bragg peak and Spread-out Bragg peak [3].

Figure 4. Three field irradiation radiotherapy scheme and corresponding overlaid isodose distribution. Red area represent a tumor [4].

Figure 5. Stereotaxic radiosurgery irradiation scheme and corresponding isodose distribution [4].
However, for quite large tumors the number of possible irradiation directions is becoming insufficient and thus requires treatment in several sessions. Other limitations of multi field irradiations are heterogeneous tumors with alternating healthy and tumor tissues regions and tumors located in close vicinity of radiosensitive critical organs. All these limitations of conventional radiotherapy can be easily overcome by another approach namely Binary Radiotherapy (BRT). Instead of increasing exposure of a tumor to ionizing radiation as it is done in conventional radiotherapy, absorbing capability of tumor tissues relatively to surrounding healthy tissues is increased in BRT. Increase of tumor’s capability to absorb external radiation is provided by special tumor specific pharmaceuticals containing dose enhancing agent (DEA), i.e. atoms of particular chemical element or isotope capable to absorb radiation much more effectively than other elements of biological tissue like hydrogen, nitrogen, carbon, oxygen and others. Selective uptake of a pharmaceutical with DEA in a tumor causes selective increase of its absorbing capability and thus creates absorbed dose preferably in the tumor region. Currently such binary approach was implemented in two BRT modalities that is Neutron Capture Therapy (NCT) and Contrast Enhanced Radiotherapy (CERT). NCT uses thermal neutrons as external ionizing radiation and isotopes with large value of neutron capture cross section such as $^{10}$B, $^{157}$Gd, $^7$Li and many other as DEA. CERT is respectively using orthovoltage X-rays and heavy elements like iodine, gold, gadolinium, hafnium and bismuth. General workflow of treating a patient with BRT looks like the following. A patient is infused or injected with tumor specific pharmaceutical containing certain DAE. The pharmaceutical is distributed in the patient’s body with sufficient selective uptake by the tumor. When maximum DEA content in the tumor and the ratio of DEA concentrations in the tumor and surrounding tissues is achieved then irradiation of the tumor region with some margins around the tumor is performed. The exposure time of irradiation is selected not to damage superficial and surrounding tissues. If DEA uptake in the tumor was high enough then curing effect is achieved. Next practical implementation of this binary approach to cure patients with ionizing radiation is described.

2. Physical basis of BRT modalities

NCT is based, as it could be guessed from its denomination, on the physical phenomenon of thermal neutron capture by nuclei. Phenomenon of neutron absorption by nuclei is possible only for thermal neutrons with energy no higher than 0.025 eV. Fast neutrons cannot be captured by nuclei and they interact with matter by elastic and inelastic scattering, which poorly depends on the soft tissue composition. Thus only thermal neutrons are suitable for NCT implementation and selective absorbed dose delivery to a target by binary approach. Neutron absorption by a nucleus of some isotope transfers the nucleus to unstable state and cause its decay with emission of ionizing radiation. The probability of this phenomenon varies greatly for different isotopes and is described by the value of neutron capture cross section ($\sigma$) measured in barns. Neutron capture cross section values for some biologically relevant isotopes as well as some DEA for NCT are presented in table 1. Some isotopes like $^{10}$B or $^{157}$Gd have very large value of neutron cross section, which is 3-5 orders larger than for major isotopes of biological tissues like hydrogen, carbon, oxygen and others. Thus presenting in a tumor the nuclei of $^{10}$B or $^{157}$Gd absorb $10^3$-10$^5$ time more neutrons then other nuclei of soft tissues and thus the region containing $^{10}$B or $^{157}$Gd receives larger absorbed dose value. It is that difference in thermal neutrons interaction with different isotopes which allows changing absorbing capability of irradiated target by adding DEA nuclei in it. Schemes of nuclear reactions induced by neutron capture by $^{10}$B or $^{157}$Gd are presented in figures 6 and 7. $^{157}$Gd has significantly larger cross section value ($\sigma=254,000$ barns) than $^{10}$B ($\sigma=3880$ barns). But $^{10}$B has more favorable nuclear reaction induced by neutron capture. Neutron capture by $^{157}$Gd leads mostly to emission of high-energy gamma-radiation (figure 7) which escapes from the target without any significant transfer of energy to it. In contrast neutron capture by $^{10}$B cause nuclear reaction with short range high-LET radiation like alpha-particle and charged heavy ion of $^7$Li, which range in water or soft tissue is less than 10 nm and comparable with the size of a tumor cell. Besides such precise energy deposition of $^{10}$B(n,$\alpha$)$^7$Li neutron capture reactions in the target volume its products i.e. alpha-particle and charged ion of $^7$Li are high-LET types of radiation with relative biological effectiveness larger than
of photons and thus creating addition damage of tumor cells per absorbed energy unit comparing to photons. That all make $^{10}$B the most usable isotope as DEA for NCT. But $^{157}$Gd shouldn’t be rejected at all, because it has completely different chemical properties which give additional opportunities in developing new gadolinium containing pharmaceuticals. Also $^{157}$Gd huge neutron capture cross section value compensate its less efficient corresponding nuclear reaction and provides sufficient tumor suppression in NCT [6]. Being a high-Z element gadolinium can serve as DEA in both BRT modalities NCT and CERT [7,8] thus giving $^{157}$Gd additional commercial advantage.

Table 1. Neutron capture reaction cross section value for some isotopes relevant to biological soft tissues and NCT DEA isotopes.

| Isotope | Cross section (barn) |
|---------|----------------------|
| $^1$H   | 0.332                |
| $^{12}$C | 0.0035              |
| $^{14}$N | 0.075               |
| $^{16}$O | 0.00019             |
| $^{10}$B | 3880.0              |
| $^{157}$Gd | 257 000.0         |

\[7\text{Li} (0,84 \text{ MeV}) \xrightarrow{93,7\%} \gamma (0,478 \text{ MeV})\]

\[n + ^{10}\text{B} \xrightarrow{Q= 2,79 \text{ MeV}} \alpha (1,47 \text{ MeV})\]

Figure 6. $^{10}$B(n,α)$^7$Li nuclear reaction scheme.
Figure 7. $^{157}\text{Gd}(n,\gamma)^{158}\text{Gd}$ nuclear reaction scheme.

Absorbed dose created by NCT in irradiated object consists of the following several components independently on the used DEA:

\[ D = D_{\text{fn}} + D_{\text{Np}} + D_{\gamma} + D_{\text{H}} + D_{\text{DAE}} \]

- $D_{\text{fn}}$ - fast neutron absorbed dose created by fast neutrons, which are inevitably present in an epithermal or thermal neutron beam. Fast neutrons are harmful and undesired for NCT and their number in the overall flux of neutrons must be reduced, as much as reasonable possible. Fast neutrons input to the total dose must be less than $2 \times 10^{-13}$ Gy per flux unit of epithermal/thermal neutrons [9].

- $D_{\text{Np}}$ – absorbed dose from nuclear reaction $^{14}\text{N}(n,p)^{14}\text{C}$, which is often referred as “nitrogene dose” or “proton dose” because neutron capture by $^{14}\text{N}$ cause emission of protons.

- $D_{\gamma}$ – photon radiation dose, which is created by gamma-radiation contamination of the neutron and must be reduced as much as possible and should be less than $2 \times 10^{-13}$ Gy per flux unit of epithermal/thermal neutrons [9].

- $D_{\text{H}}$ - absorbed dose from nuclear reaction $^1\text{H}(n,\gamma)^2\text{H}$, which is referred as “hydrogen” dose.

- $D_{\text{DAE}}$ – absorbed dose from neutron capture nuclear reaction on DEA. This dose depends on DEA concentration in the target and is the main tool to provide targeted dose delivery into a tumor.

$D_{\text{fn}}$ and $D_{\gamma}$ are undesirable components for NCT as they provide non-tissue-specific dose equally on normal and tumor tissues and these two components should be minimized. $D_{\text{Np}}$ and $D_{\text{H}}$ are also delivered equally to tumor and healthy tissues but they are produced by thermal neutrons and cannot be removed as nitrogen and hydrogen are inherently distributed almost uniformly around human’s body. The only way in NCT to perform required delivery of therapeutic absorbed dose value is to make DEA dose large enough to make other component negligible. Absorbed dose components calculations made by a group of Finnish scientists for epithermal neutron beam of FiR1 nuclear reaction, which was used in Clinical Trials of NCT showed that for $^{10}\text{B}$ concentration of 15 ppm the DEA dose becomes equal to the sum of the rest of the components and comprises 50% of the total absorbed dose in NCT [10]. That means that if tissues surrounding the tumor with boron content of 15 ppm contain no boron, then the absorbed dose value in the tumor would be twice larger than in surrounding tissues and thus 15 ppm $^{10}\text{B}$ concentration can be considered as the theoretical minimum threshold of NCT efficacy with $^{10}\text{B}$ as DEA. For concentration of $^{10}\text{B}$ over 50 ppm corresponding DEA dose will be over 80% of the total dose and that means that therapeutic dose is created only at the sites with such high boron content. From these facts the main requirements for boron carrier pharmaceutical can be revealed:

1. NCT pharmaceutical must deliver $^{10}\text{B}$ to a tumor in concentration higher than 15 ppm.
2. The selectivity of NCT pharmaceutical biodistribution must create the ratio of concentration in tumor and normal tissues (T/N ratio) higher than 3.
Thus using boron carrier pharmaceutical with such prescribed properties NCT can cure different types of tumors, which cannot be effectively treated with other therapeutic modalities. For $^{157}$Gd the requirement of T/N ratio over 3 is also valid, but the absolute minimum concentration of $^{157}$Gd in tumor is still undetermined.

CERT uses photoabsorption phenomenon as physical basis to implement BRT approach. If one takes a look to the mass energy absorption coefficient ($\mu_{\text{en}}$) distribution of different chemical elements and media by incident photon energy (figure 8) then it can be seen that in the range of photon energies from 10 keV to 300 keV (kilovoltage and othovoltage X-rays) there is a significant difference in absorbing capability between soft tissue and such elements as iodine, gadolinium, gold, bismuth and others which can be roughly distinguished as elements with Z>52 or high-Z elements.

**Figure 8.** Mass energy absorption coefficient ($\mu_{\text{en}}$) distribution of different chemical elements and media by incident photon energy.

That difference allows such elements to serve as DEA for CERT. In CERT it is convenient to express dose enhancement using dose enhancement factor (DEF) which is the ratio of absorbed dose in the object in case of DEA present in its content and without it:

$$\text{DEF}(C) = \frac{D(C)}{D_0},$$

where D(C) is absorbed dose value for DEA concentration in the irradiated object of C and D$_0$ is absorbed dose value for the same object but without DEA (C=0 mg/mL). Calculated [11,12,13] and measured [14,15] DEF values show that DEF of 2 can be achieved by DEA concentration in the range of 10-20 mg/mL depending on the Z value of the particular DEA and energy spectrum of the incident x-ray radiation [16].

In contrast to NCT where nuclear energy release happens and brings additional energy to the absorbed dose from nuclear bonds in CERT only redistribution of the incident photon energy occurs causing its absorption at the site of DEA location. However, CERT practical implementation is much simpler and cheaper than NCT’s one [13, 17].
3. Pharmaceutical basis and Clinical application of BRT modalities

Described above physical principles of BRT make it obvious that the key to successful application of BRT is an availability of tumor specific pharmaceuticals capable to deliver necessary amount of DEA to tumor and at the same time supply as less DEA in surrounding tissues as possible by the time of beginning the irradiation.

Huge number of different boron-containing substances from simple boric acid to complicated boron conjugates and nanoparticles were tested for NCT [18]. However only two substances proved their therapeutic efficacy in NCT namely (L)-4-dihydroxy-borylphenylalanine or BPA and sodium mercaptoundecahydro-closo-dodecaborate or BSH (figure 9 and 10) and only BPA in 2020 in Japan was approved as a pharmaceutical called Steboronine® (Stella Pharma, Japan).

Figure 9. Structural chemical formula of (L)-4-dihydroxy-borylphenylalanine (BPA).

Figure 10. Structural chemical formula of mercaptoundecahydro-closo-dodecaborate (BSH).

BSH was introduced into NCT Clinical Trials of brain tumors earlier than BPA. NCT with BSH of patients with primary brain tumors surgically removed 1 month prior NCT showed 5-year survival 7.2 % and 10-year survival 4.8 % of patients with glioblastoma and 5-year survival 31.8 % and 10-year survival 8.8 % of patients with astrocytoma [19]. BSH has very high boron content of 55% and excellent solubility in water but its main shortcoming is lack of uptake by tumor comparing to BPA. Tumor–to-blood ratio rarely exceed 1 [20,21] thus inevitably leads to excessive damage of blood vessels in the neutron irradiation field. BPA is more successful and efficient as a drug for NCT than BSH. Recent NCT with BPA Clinical Trials showed 1-year survival 79.2 % and 100% of patients with recurrent gliomas and head and neck cancer respectively [22,23]. Despite of that BPA is still not the ideal boron carrier for NCT. BPA even in complex with fructose or sorbitol has very low water solubility and requires infusion to patient of 600 - 1500 mL of the solution. Being used in dose more than 500 mg/kg can cause formation of BPA crystals in kidneys thus causing possible renal insufficiency. However, BPA is still the only NCT boron pharmaceutical which showed unique NCT efficacy in curing malignant tumors [24,25].

From the pharmacy point of view CERT is luckier than NCT because iodine and gadolinium contrast drugs for CT and MRI are commercially available and were introduced into routine clinical practice long ago. Indeed, iodine contrast drug Isovue-300TM was used in the first CERT Phase I Clinical Trials of brain tumors in USA [26]. Iodine contrast drugs shows acceptable uptake by brain tumor because of blood-brain barrier disruption [26,27]. Being irradiated with modified CT scanner after iodine contrast drug injection all the patient involved in the trial well tolerated the treatment and in some patients good local control of tumor was achieved. Another Clinical Trials of brain tumors CERT with conventional iodine contrast drugs were started in 2012 in France on European Synchrotron Facility [28]. This trials are still in progress and the results are forthcoming. Iodine CT contrast drugs have very high iodine content (up to 400 mg/mL) and are well tolerated by patients but have very low specificity to tumors and can be used only for some brain tumors. More promising for CERT are drugs based on high-Z nanoparticles like gold nanoparticles or gadolinium polymeric nanoparticles like AGUIX [29]. Nanoparticles showed excellent uptake and retention for different types of tumors and are well tolerated.
being injected intravenously [30,31,32,33]. The major question of nanoparticles application in CERT is their excretion and enormous uptake by liver and spleen, which lasts for several months and may be even years and which can cause undesired long-term complications within the patient. However, for oncological patients with poor prognosis that could be a salvation prolonging their life and improving quality of life.

4. Conclusion
BRT is a powerful approach yet underestimated so far to improve the efficacy of ionizing radiation application in curing malignant tumors and extend it to wide range of tumor nosologies. BRT can overcome inherent limitations of conventional beam radiotherapies and cure radioresistant tumors, heterogeneous invasive tumors close to critical organs and multi lesion disseminated neoplasms. BRT combines advantages of beam radiotherapy and radionuclide radiotherapy. BRT pharmaceuticals with DEA are not radioactive and do not damage normal organs while distributed and excreted. But they become the source of secondary short range radiation when being irradiated with external beam of corresponding radiation. BRT has the possibility of self targeting using specific physiological and biochemical properties of tumor lesions by selective uptake of DEA only in tumor region. Despite of quite complex multidisciplinary implementation of BRT its selftargeting possibility makes these methods inherently safer and less dependent on diagnostic, treatment planning and patient positioning errors. Potential of pharmaceuticals for BRT is still unrevealed and the progress in this area of research and development could really make a brakethrough in solving the problem of fighting cancer.

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