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Editorial

Interdisciplinary Approaches for Oncological Treatments: Proton Therapy at the Intersection of Physics and Medicine

Interdisciplinarni pristopi k onkološkim zdravljenjem: Protonska terapija na presečišču fizike in medicine

Key words

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The inspiration for writing this editorial came from a recent visit to the European Organization for Nuclear Research (CERN, Conseil Européen pour la Recherche Nucléaire) in Geneva. There I had the opportunity to take a closer look at the technology of proton production and acceleration in cyclotrons. I was impressed by this direct insight into physical findings that have an impact on many other scientific fields. I learned how these scientific discoveries are used in medicine, especially in oncology, and how this interdisciplinary approach can improve patients' lives. This experience gave me a new perspective and encouraged me to research and write about this important and innovative field. In the following, we will explore how proton therapy has changed the way and success of treatments in oncology and how the interdisciplinary collaboration between physics and medicine has contributed to this progress. In addition, I have focused on the relevance of this technology to veterinary medicine and the potential it offers for improving cancer treatment in our pets.

The technology for accelerating protons was developed at the beginning of the 20th century. Protons were discovered in 1919 (1). The first large proton synchrotron was the

Navdih za pisanje tega uredniškega članka je nastal z nedavnim obiskom Evropske organizacije za jedrske raziskave (CERN, Conseil Européen pour la Recherche Nucléaire) v Ženevi. Tam sem imela priložnost pobliže spoznati tehnologijo pridobivanja protonov in njihovega pospeševanja v ciklotronih. Ta neposreden vpogled v fizikalno znanje, ki seva v mnoga druga znanstvena področja, me je navdušil. Spoznala sem, kako se ta znanstvena odkritja uporabljajo v medicini, zlasti v onkologiji, in kako lahko ta interdisciplinarni pristop izboljša življenja bolnikov. Ta izkušnja mi je dala novo perspektivo in me spodbudila k raziskovanju in pisanju o tem pomembnem in inovativnem področju. V nadaljevanju bomo raziskali, kako je protonska terapija preoblikovala način in uspešnost zdravljenj v onkologiji in kako je interdisciplinarno sodelovanje med fiziko in medicino prispevalo k temu napredku. Pri tem sem se osredotočila o pomenu te tehnologije za veterinarsko medicino in kakšen potencial predstavlja pri izboljšanju zdravljenja raka pri naših ljubljenčkih.

Tehnologija pospeševanja protonov se je začela razvijati v zgodnjem 20. stoletju. Protoni so bili odkriti leta 1919

Cosmotron at Brookhaven National Laboratory, which accelerated protons to about 3 GeV (2). CERN played an important role in the development of proton acceleration technology. Their Proton Synchrotron (PS) there accelerated protons for the first time in 1959 and was briefly the most powerful particle accelerator in the world (3). The PS was CERN's first synchrotron and was initially CERN's main accelerator. When the laboratory built new accelerators in the 1970s, the main task of the PS became to supply these accelerators with particles. The Super Proton Synchrotron (SPS) was built after the PS and served as the main accelerator for several years until the Large Hadron Collider (LHC) was built. The Large Electron-Positron Collider (LEP) was built in the same tunnel that now houses the LHC and was the largest electron-positron collider in the world. The LHC is currently the largest and most powerful particle accelerator in the world (4). In accelerators, protons are accelerated to speeds of up to 60% of the speed of light (5) with the help of powerful magnets. This allows protons to reach enormous amounts of energy, up to 230 million electron volts (6).

The idea of using protons for medical treatment was first proposed in 1946 by the physicist Robert R. Wilson (7). Wilson suggested that protons could be used to deliver a precise dose of radiation to tumors while protecting the surrounding healthy tissue. Proton therapy is therefore a form of radiotherapy in which charged particles, protons, are used to irradiate cancerous tissue. With a speed of up to 60 % of the speed of light, protons gain so much energy that they can penetrate about 32 g/cm², which enables the treatment of tumors located deep in the body (8). The unique physical properties of protons allow precise control of the irradiation depth and intensity, making proton therapy ideal for treating brain tumors located near important neuronal structures, for example (9).

The first attempts to treat patients with proton beams began as early as 1954 at the Lawrence Berkeley National Laboratory in California, USA (10). In the same year and in the same laboratory, proton therapy was also used for the first time to treat animals, namely a dog with breast cancer (10). The dog's pituitary gland was removed by radiosurgery using proton beams, and the dog lived for at least two years after the treatment. However, it was not until the late 1970s, when advanced imaging technologies, sophisticated computers and improved accelerator technology were developed, that proton therapy could be used for routine medical and veterinary applications. Today, proton therapy is used in human medicine to treat various types of cancer, and there are proton therapy centers around the world that offer this advanced form of radiation therapy. Unfortunately, medical facilities in Slovenia do not yet offer proton therapy (11, 12). The closest center for irradiating cancer patients with protons is MedAustron near Vienna (13). Proton therapy has also become an important part of veterinary oncology. There are not as many documented examples of its use in veterinary medicine in the literature as there is an extensive database for human medicine. However, the data shows that it is most commonly used or researched for the treatment of cancer

(1). Prvi veliki protonski sinhrotron je bil Cosmotron v Brookhaven National Laboratory, ki je pospešil protone do približno 3 GeV (2). CERN je imel pomembno vlogo pri razvoju tehnologije pospeševanja protonov. Njihov Proton Synchrotron (PS) je prvič pospešil protone leta 1959 in za kratek čas postal najmočnejši delcev pospeševalnik na svetu (3). PS je bil prvi sinhrotron CERN-a in je bil sprva glavni pospeševalnik CERN-a. Ko je laboratorij v 70-ih letih prejšnjega stoletja zgradil nove pospeševalnike, je glavna vloga PS postala dobava delcev le-tem. Super Proton Sinhrotron (SPS) je bil zgrajen po PS in je služil kot glavni pospeševalnik več let, dokler ni bil zgrajen Veliki hadronski trkalnik (LHC). Large Electron-Positron Collider (LEP) je bil zgrajen v istem tunelu, kjer se danes nahaja LHC in je bil največji elektron-pozitronski trkalnik na svetu. LHC pa je trenutno največji in najmočnejši pospeševalnik delcev na svetu (4). V teh pospeševalnikih se protone s pomočjo mogočnih magnetov pospeši do hitrosti, ki dosežejo do 60% hitrosti svetlobe (5). To omogoča, da protoni dosežejo ogromne količine energije, do 230 milijonov elektron voltov (6).

Ideja o uporabi protonov za medicinsko zdravljenje je prvič vzniknila leta 1946 s strani fizika Roberta R. Wilsona (7). Wilson je predlagal, da bi se protoni lahko uporabljali za natančno doziranje sevanja na tumorje, pri čemer bi varovali okoliško zdravo tkivo. Protonska terapija je tako oblika radioterapije, ki uporablja nabite delce, protone, za usmerjeno oddajanje sevanja na rakavo tkivo. Pri hitrosti do 60 % svetlobne hitrosti protoni dobijo tako veliko energije, da lahko prodrejo približno 32 g/cm² globoko v telo, kar omogoča zdravljenje tumorjev, ki so globoko v telesu (8). Edinstvene fizikalne lastnosti protonov omogočajo natančen nadzor nad globino in intenzivnostjo sevanja, zaradi česar je protonska terapija idealna na primer za zdravljenje možganskih tumorjev, ki so blizu ključnih nevralnih struktur (9).

Prvi poskusi uporabe protonskih žarkov za zdravljenje bolnikov so se začeli že leta 1954 v Nacionalnem laboratoriju Lawrence Berkeley v Kaliforniji, ZDA (10). V istem letu in v istem laboratoriju se je protonska terapija prvič uporabila tudi za zdravljenje živali in sicer pri psu z rakom dojk (10). Pri psu so z radiokirurgijo odstranili hipofizo z uporabo protonskih žarkov, in pes je po zdravljenju živel vsaj še 2 leti. Vendar pa je bilo šele v poznih 70. letih, ko so se razvile napredne tehnologije slikanja, sofisticirani računalniki in izboljšana tehnologija pospeševalnikov in je bilo protonsko terapijo mogoče uporabljati za rutinske medicinske in veterinarske aplikacije. Danes se v humani medicini protonska terapija uporablja za zdravljenje različnih vrst rakov, in po vsem svetu obstajajo centri za protonske terapije, ki ponujajo to napredno obliko radioterapije. Žal v Sloveniji medicinske ustanove protonske terapije še ne ponujajo (11, 12). Nam najbližji center za obsevanje bolnikov z rakom s protoni je MedAustron pri Dunaju (13). Tudi v veterinarski onkologiji je protonska terapija postala pomemben del. V literaturi sicer ni toliko dokumentiranih del uporabe v veterinarski medicini, kakor je baza obširna za humano medicino. Podatki pa kažejo, da se najpogosteje uporablja oziroma raziskuje za

in dogs. With normal radiation, dogs survive on average 2 to 4 months. With proton therapy, survival time is extended because less damage is done to healthy tissue and the tumor is irradiated with more energy than with conventional radiation. It is also believed that proton therapy improves the dog's immune response to the tumor (14). Although proton therapy is still considered a new therapy in veterinary medicine, it is spreading rapidly and the technology is constantly being developed and improved.

Crucial to the development of proton therapy are preclinical studies that contribute to the understanding and improvement of this advanced method of cancer treatment. These studies include research on laboratory animals and cell models to better understand the effects of proton beams on tumor cells and surrounding healthy tissue. Preclinical studies are also helping to develop more precise and effective methods for using proton beams that can improve treatment outcomes (15). In the preclinical phase, there are also studies investigating combined radiation. In the study by Rozanova et al. (2022), they investigated the effects of combined proton and neutron irradiation on the solid form of ascitic Ehrlich carcinoma on tumor response and skin reactions in mice bearing the tumor (16). They found that irradiation of mice with neutrons both before and after irradiation with protons effectively inhibited the growth of the carcinoma one month after exposure. Based on the frequency and severity of skin lesions observed in mice 15–40 days after therapy, neutron irradiation after proton irradiation significantly improved these indicators compared to exposure to proton beams alone; however, neutron irradiation before proton irradiation showed more damage than the other variants. They also showed that the incidence of tumor recurrence was significantly higher and overall survival lower in the groups of animals with combined irradiation than in the group of mice irradiated with protons alone. In addition, preclinical studies are key to exploring and resolving some unresolved issues in proton therapy, such as the relative biological effectiveness (RBE) of protons. All preclinical research thus forms the basis for clinical studies and the further development of proton therapy.

In oncology, innovative therapeutic options are constantly being sought to improve the precision of tumor treatment. Proton therapy, which emerged from cutting-edge physics research, has established itself as a revolutionary medical procedure that offers unprecedented precision in the irradiation of tumors. In addition to its use in human medicine, proton therapy is also of great importance in veterinary medicine. Thanks to the precision it offers, veterinarians can treat tumors in animals in a more targeted way, reducing side effects and improving the quality of life of our pets. This interdisciplinary approach, which combines physics and medicine, therefore promises major advances in the treatment of cancer in humans and animals.

zdravljenje raka pri psih. Pri prejemanju običajnega obsevanja, psi v povprečju preživijo 2 – 4 mesece. S protonsko terapijo pa se dobo preživetja podaljša, saj nastane manj poškodb zdravega tkiva, tumor pa je obsevan z večjo energijo kot pri običajnem obsevanju. Poleg tega naj bi protonska terapija izboljšala imunske odzive psa proti tumorju (14). Čeprav še vedno velja za novo terapijo, se uporaba protonske terapije v veterinarski medicini hitro širi, tehnologija pa se neprestano razvija in izboljšuje.

Za sam razvoj protonske terapije so ključne predklinične raziskave protonske terapije, ki doprinašajo k razumevanju in izboljšanju te napredne metode zdravljenja raka. Te raziskave vključujejo študije na laboratorijskih živalih in celičnih modelih, da bi bolje razumeli učinke protonskih žarkov na tumorske celice in okoliško zdravo tkivo. Predklinične raziskave prav tako pomagajo pri razvoju natančnejših in učinkovitejših načinov dostave protonskih žarkov, kar lahko izboljša rezultate zdravljenja (15). V predklinični fazi so tudi študije, ki raziskujejo kombinirano obsevanje. V študiji Rozanova in sod. (2022) so raziskovali učinke kombiniranega obsevanja s protoni in nevtroni na trdni obliki ascitskega Ehrlichovega karcinoma na odziv tumorja in reakcije kože pri miših (16). Ugotovili so, da je obsevanje miši z nevtroni tako pred kot po obsevanju s protoni učinkovito zaviralo rast karcinoma v enem mesecu po izpostavljenosti. Glede na pogostost in resnost poškodb kože, opaženih pri miših 15–40 dni po terapiji, je obsevanje z nevtroni po obsevanju s protoni privedlo do pomembnega izboljšanja teh kazalnikov v primerjavi z delovanjem samo protonskih žarkov; vendar pa je obsevanje z nevtroni pred protoni izkazalo večjo škodo kot v drugih variantah. Prav tako so pokazali, da je bila pogostost ponovitve tumorja v skupinah živali z kombiniranim obsevanjem bistveno višja, skupna življenjska doba pa nižja v primerjavi s skupino miši, ki so bile obsevane samo s protoni. Predklinične raziskave so ključne tudi za raziskovanje in reševanje nekaterih nerešenih vprašanj v protonski terapiji, kot je relativna biološka učinkovitost (RBE) protonov. Raziskave na predkliničnem nivoju so tako temelj za klinične študije in nadaljnji razvoj protonske terapije.

V onkologiji se nenehno iščejo inovativne terapevtske možnosti, ki bi izboljšale natančnost ciljanja tumorjev. Protonska terapija, ki izhaja iz naprednih fizikalnih raziskav, se je uveljavila kot revolucionarna medicinska metoda z neprekosljivo natančnostjo pri obsevanju tumorjev. Poleg uporabe v humani medicini, ima protonska terapija pomemben pomen tudi v veterinarski medicini. Z natančnostjo, ki jo omogoča, lahko veterinarji bolje ciljajo na tumorje pri živalih, kar zmanjšuje stranske učinke in izboljšuje kakovost življenja naših ljubljenčkov. Ta interdisciplinarni pristop, ki združuje fiziko in medicino, tako obeta velik napredek v zdravljenju raka tako pri ljudeh kot pri živalih.

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