Radiation Therapy

Subjects: Oncology

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Tumor radioresistance is associated with a failure to achieve loco-regional disease control following radiotherapy with the highest acceptable doses. Radiobiology research focused on tumor radioresistance has pointed out several mechanisms attenuating the efficacy of tumor irradiation and several treatment answers to overcome such radio-resistance. Personalized medecine allows us to adapt the treatment to diseases according to patient specificities and characteristics. Novel radiotherapy such as heavy ion therapy enable a better balance between high doses to the tumor and low doses to the surrounding healthy tissues.

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1. Proton Therapy in Tumor Control

In contrast to conventional radiotherapy using photons, proton therapy (PT) uses charged particles that are roughly 2000 times heavier than electrons. PT can be used to: i) reduce the exposure of healthy normal tissues, and thus, lower the risk of toxicity, without any attempt to increase the dose to the target, and ii) increase the dose to the target volume to improve the likelihood of tumor control, while maintaining doses under the limits of tolerance in surrounding tissues.

These advantages are related primarily to the physical interactions of accelerated particles with matter: unlike x-rays (photons), which attenuate exponentially, with inevitable dose-deposition along their path, particles (such as protons and carbon ions) have a finite range and deposit most of their energy at the end of their range, commonly described as the “Bragg peak” (BP). These properties translate into a sharp decline in doses beyond the target, and no “exit” doses.

PT has been used since the late 1950s for rare malignancies that were radioresistant, such as ocular melanomas and skull-base sarcomas. Such cancer locations were in close proximity to critical anatomical structures, which prevented radical resection, which is otherwise highly mutilating, and proper dose coverage using conventional (i.e., x-ray) irradiation. PT has become the standard practice for ocular melanomas since the 1990s, effecting > 95% local control[1]and ≥ 75% eye preservation rates[2]. Conventional x-ray irradiation of skull base tumors has been limited to infracurative doses of 60 Gy due to the proximity of critical structures (primarily the optic pathway and brain stem). Safely delivered proton doses of 70 Gy CGE [cobalt Gray equivalent = physical dose × estimated mean 1.1 RBE (relative biological efficiency), now specified as “Gy (RBE)”] reproducibly achieved > 70% 5-year local control using passively delivered PT compared with ≤ 40% with conventional irradiation[3][4]. Outcomes with radioresistant and poorly limited, rapidly proliferating glioblastomas have been less favorable.

Data on tumor progression in areas that have received less than 70 Gy (RBE)[5]have not been reproduced; however, higher doses are highly toxic to the brain[6]. The introduction of rotating gantries in PT in the mid-1990s and, more recently, the active scanning mode has made common extracranial tumors more accessible to PT.

The spatial distribution of protons thus allows efficient irradiation of radioresistant tumors, but mature results and randomized trials are awaited[7]. The distal section of PT beams, targeting the immediate surrounding layer of tissues at the border of the tumor, might experience a significant increase in LET, causing unwanted toxicities that limit dose escalation and control of radioresistant tumors. Thus, regarding clinical radiobiology, the constant generic 1.1 RBE value, which has been adopted worldwide for PT, might be invalid at the distal part of the Spread-Out Bragg Peak (≈ 1.4 RBE), in relation to increased LET.

Despite the limited impact on tumor control, these variations could have a significant impact on toxicity and might contribute to unusual CNS (central nervous system) radiological and clinical abnormalities following PT[8]. Consequently, several reports have stressed the importance of Monte Carlo calculation models, LET cartography, and individual sensitivity with regard to dose escalation and more active treatment of radioresistant cases[9]. Beyond calculation and

simulation tools, experimental studies must be performed to accurately compare the bioeffectiveness of protons and other beams and between various types of proton beams, such as scattered beams and the more recent scanned beams. The endpoint could be to express the relationship between beam physics and biology as mathematical models.

Innovations in particle therapy (e.g., robotized gantries and couches, embarked image-guidance, motion-gating, beam intensity modulation, arc therapy, improved calculation algorithms) will allow refined and differentiated tumor coverage, including dose painting (i.e., significant dose escalation) in radioresistant areas, such as hypoxic regions, while sparing normal tissues[10].

However, considering the lack of true enhanced RBE of PT in the tumor, pushing the effectiveness of PT beyond dose escalation will need to consider, as done historically for x-rays, the introduction of combined modalities that specifically radiosensitize tumor cells. Thus, the differential effect between the tumor and extremely close or even tumor-embedded normal tissues and organs (primarily small nervous structures, nerves, and blood vessels) will increase. Moreover, PT could alleviate the global toxicity of combined modalities by dramatically limiting the synergistic systemic toxic effects due to the reduction and near-avoidance of any out-of-field dose[11]. Present experience shows that any chemotherapy that has been validated in combination with x-rays is manageable when coupled with PT[12]. Thus, recent advances are likely to develop further with innovative approaches, such as nanoparticles[13], targeted therapies, and immunotherapy[14][15], as developed in Section 4 of this paper.

To improve our ability to identify eligible patients for advanced PT procedures, especially regarding radioresistant tumors, we must dramatically improve prediction tools, such as the tumor control probability (TCP) and normal tissue complication probability (NTCP) models, advancing toward multiparametric models that incorporate patient- and tumor-specific parameters. To evaluate, consolidate, and validate these models, randomized studies, or at least large cohorts of patients with long-term follow-ups, will be necessary.

2. Hadrontherapy: Carbon Ions and Multi-Ion Therapy

In addition to prevailing over the physical advantages of protons, carbon ions have greater radiobiological efficacy compared with photons and protons. A strong relationship has been established between ionizing density as measured by the LET and the RBE of ionizing radiation. Low-energy photons (used only for very superficial tumors) and slow charged particles have much higher LET values than the currently used megavoltage photons. The ratio can reach approximately 1000, with values of between 0.3 and 200 keV/µm.

For example, protons that are used for deep-seated tumors have LET values of roughly 0.3 keV/µm (as do megavoltage photons) in their entrance channel and reach approximately 5–20 keV/µm in the distal fall-off region. For carbon ions, these values are ~10 and over 85 keV/µm, respectively. This high LET of carbon ions impacts several biological characteristics of cellular and tissue responses, such as the enhanced killing effect on normal oxygenated tissues (as evidenced by RBE) and hypoxic tissues (based on the OER) that are otherwise extremely radioresistant to low-LET radiation, which has been observed for decades[16].

The ability of high-LET ions to overcome resistance also develops by increasing cell death through the extrinsic ceramide apoptotic pathwa[17]and killing telomerase-activated cells[18]. Controversial observations have been reported regarding the level of oxidative stress with high-LET ions in tumor cells. The physiological oxygen tension of the irradiated tissue must be considered to measure the actual oxidative stress that is generated by irradiation at various LETs[19][20]. Hypoxic cells have expressed little or no HIF after ion irradiation compared with photon irradiation, which could be linked to less radioresistance; this observation is also seen under normoxic conditions[20]. These radiobiological responses can enhance the radiosensitivity to ions, in addition to the physicochemical characteristics of their dense ionizing tracks, which can explain the more complex and less reparable DNA damage that is more cytotoxic[21]. A unifying hypothesis of these effects is that more localized, and thus less diffuse, oxidative stress, although dense in the ion tracks, induces complex DNA damage but fewer radiation-induced tumor escape mechanisms.

Tumor cells that are irradiated by ions are less prone to invasion and mobility and switch to a stem cell-like phenotype (CSCs)[22]. CSCs have been implicated in tumor invasion, cancer recurrence, and radioresistance, but how these CSCs should be targeted efficiently remains unknown[23]. Conventional radiotherapy (x-rays) induces an adaptive response in tumors and their microenvironment, which might promote cellular plasticity and thus induce CSC properties in non-CSCs and, ultimately, radiation resistance. This specific response could be mitigated by high-LET irradiation[24].

High-LET beams have enhanced effects on living cells with limited specificity toward tumor cells. Consequently, their application is strictly limited by the tolerance of healthy tissues and is only feasible due to the highly conformal irradiation that is allowed by their finite path and the Bragg peak. However, the unavoidable entrance channel dose is an important

parameter of dose and toxicity. The heavier and more highly charged the ion is, the higher the LET will be in the entrance before the Bragg peak. Thus, deep tumors that are treated through long entrance channels must be administered a beam with an entrance LET that is as low as possible while maintaining a high LET in the SOBP. Carbon ions supply a low-LET entrance channel and a high LET in the SOBP. Certain resistant tumors and more superficial tumors could be treated by heavier particles than carbon ions, such as oxygen and neon ions, or combinations of high- and lower-LET particles according to the principles of biologically guided therapy and dose painting. Heavier ions would be preferentially directed to hypoxic tumor areas, whereas lighter ions would deliver the remaining dose to normoxic regions[25]. Overcoming the technical challenges of multi-ion beam sessions is one of the aims for the C400 multi-ion cyclotron (French ARCHADE project).

3. Ultra-High-Dose-Rate FLASH Proton Therapy

Compared with the conventional RT doses and dose rates in clinical practice (on the order of less 0.5 Gy per second for a 2-Gy session), FLASH radiotherapy (FLASH-RT) uses an ultra-high dose rate (originally described as above 40 Gy/second but more likely reproducible above 100 Gy/second). Initial experiences have been performed with electrons, but photon and proton beams can also be used, provided that they can achieve the instantaneous high dose rate that is needed to observe a FLASH effect. Despite lobbying by proton therapy vendors, it is unknown whether current machine specifications can achieve sufficient instantaneous dose rates. The FLASH effect describes unexpected protection of normal tissue from radiation-induced toxicity in vivo[26]. Due to this sparing effect of healthy tissues, associated with an antitumor effect similar to conventional dose-rate, FLASH-RT is logically considered to be a promising means of increasing the therapeutic ratio[27], including with proton therapy. The underlying mechanisms remain incompletely understood, although a notable hypothesis is being tested and despite the clinical requirements for treating small-field superficial tumors and deep tumors using multiple beams having not been tested[28].

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