Radiation's formulations

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Radiation is not radiation is not radiation. Alternatively, one might assert that therapeutic radiation comes in such a variety of forms with sufficiently distinct physical and biological properties that clumping them together under a single moniker and assuming equivalence is at best misleading, if not preposterous. This has been apparent since the very discovery of radioactivity. These world-changing events have been meticulously recounted\textsuperscript{1,2} but please permit a cursory narrative to help illuminate modern developments. In 1895, Wilhelm Röntgen, a physicist in Würzburg, Germany, accidentally discovered that rays from a cathode tube passed through many substances leaving shadows from denser objects. He won the 1901 physics Nobel Prize. In 1902, Marie Curie and her husband, Pierre, in Paris, France, isolated radioactive radium salts from pitchblende. Together they won the 1903 physics Nobel Prize, and she alone won the 1911 chemistry Nobel Prize for the isolation of pure radium and polonium.

Teletherapy with Röntgen-rays, which Wilhelm Röntgen himself termed x-rays, and brachytherapy with radium were, once discovered, almost immediately applied to human care. Within months of Röntgen’s announcement medical uses for x-rays were intimated, and within a year had begun in earnest.\textsuperscript{3} In 1896, an American physician in Chicago, Emil Grubbe, was formally evaluating medical uses for x-rays,\textsuperscript{4} and external beam radiation treatments were underway.

Radium opened the portal for applying radiation sources directly onto or into tumors. The first reported cancer cure with such an approach dates to 1903,\textsuperscript{5} inaugurating brachytherapy, which promptly expanded to many conditions involving readily reachable regions, such as skin, nose, mouth, esophagus, anus, rectum, and vagina, but also to tumors accessed via incision.\textsuperscript{6} These separate forms of therapeutic radiation delivery (teletherapy and brachytherapy) have remained distinctive, and modern developments have broadened their idiosyncrasies. Today, an expanding array of options and indications are available or under development with very differing indications and implications, underscoring the fact that radiation is not to be viewed as a single modality with a single mode of action any more than is surgery or pharmacotherapy with their assorted forms, indications, and outcomes.

Radiation therapy (RT) options encompass many differing waves and particles, for example, x-rays, gamma rays, electrons, protons, neutrons, and carbon ions with contrasting physical and biological properties. In addition to diverse forms of radiation, endeavors to optimize therapeutic gain have produced disparate dosing intervals, cumulative doses, fraction number and timing, beam energies, target volumes, and dose rates, not even to mention striking recent developments in interdisciplinary care. With such advances, the operational descriptions of RT as well as its therapeutic goals are expanding. Higher doses may be viewed as ablative, mid-range doses perhaps subablative but immunomodulatory, and recently even lower doses as tumor microenvironment modulating, each with nuanced applications in light of multimodal therapies.\textsuperscript{7}

There is indeed some overlap in therapeutic effect among differing radiation modalities, energies, and dosing parameters, but outcomes may clearly differ, requiring separate assessment. It is simply inadequate to conclude that radiation works or does not work in a particular setting without careful consideration of the subtleties.

Despite initial successes with central nervous system (CNS) brachytherapy and the durable achievements with brachytherapy for other tumor sites, it gradually fell from favor in the CNS realm for a variety of reasons. Constructing radioactive sources and calculating doses were complex. There were legitimate concerns about the effects of radiation on physicians and staff with repeated exposure. Moreover, technological developments in teletherapy were more expeditious, resulting in de-emphasis on CNS brachytherapy at a majority of training centers.

The first recorded use of radium within an intracranial tumor was for pituitary adenoma in 1912.\textsuperscript{8,9} By 1914, brachytherapy had been employed to treat parenchymal brain tumors.\textsuperscript{10} However, even noting these early inroads, the broad application of brachytherapy to CNS tumors faltered, awaiting the atomic era with new radionuclides, the evolution of computers, advances in treatment planning, stereotaxis, and safety, all of which now provide a strong foundation for brachytherapy.

Brachytherapy remains essential in some settings and attractive in many others. Higher precisely targeted doses...
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of radiation are typically preferable, but this is constrained by the tolerance of surrounding normal brain and other critical tissues. Brachytherapy addresses these concerns by employing energies that dissipate rapidly beyond targeted tumor, the result being higher doses to the tumor and lower doses to smaller volumes of normal tissue. Brachytherapy has been used in several CNS circles, including craniopharyngioma, meningioma, metastasis, and paraspinal tumors, among others, but the most extensive CNS brachytherapy experience applies to malignant glioma. A Surveillance, Epidemiology, and End Results (SEER) database analysis reported improved median overall survival with brachytherapy of 16 months vs 9 months without \( (P < .001) \) and found that improved outcomes persisted on multivariate analysis. However, 2 randomized phase III trials, one from Laperriere et al from Princess Margaret Cancer Centre (PMCC) and the University of Toronto,\textsuperscript{13} the other from Selker et al from the Brain Tumor Cooperative Group (BTCG 8701),\textsuperscript{14} compared external beam radiation therapy (EBRT) with EBRT + brachytherapy. Both trials reported no significant survival advantage with a brachytherapy boost, although within each trial median survival was numerically modestly superior with brachytherapy, 13.8 vs 13.2 months \( (P = .49) \) in the PMCC report and more notably 68.1 vs 58.8 weeks \( (P = .101) \) with the BTCG, which also used carmustine in each study arm. The PMCC and BTCG studies both employed temporary interstitial iodine-125 \( (^{125}I) \) brachytherapy sources delivering 60 Gy over several days. A prospective study of maximum safe resection and cesium-131 \( (^{131}Cs) \) GammaTile brachytherapy for patients with recurrent glioblastoma encountered median survival of 15.1 months,\textsuperscript{15} in essence equaling the BTCG results with newly diagnosed malignant glioma, including some patients with anaplastic histology.

This edition of Neuro-Oncology examines CNS brachytherapy with emphasis on GammaTile, which employs \( ^{125}I \) sources uniformly spaced within collagen tiles placed intraoperatively so as to uniformly target at-risk areas in and around an operative bed. \( ^{131}Cs \) has a half-life of 9.7 days and emits only 29.4 keV photons with no beta radiation and, as incorporated in GammaTile is a new modality offering renewed opportunities for CNS brachytherapy. Outcome differences between \( ^{131}Cs \) and \( ^{125}I \) may arise based upon varying physical properties such as half-life and based upon implant positioning, geometry, and timing, again appreciating that radiation is not radiation is not radiation.

Dose rate matters, and may play a considerably more critical role than previously appreciated. Modern developments in RT are exploiting adaptations in dose rate with which half-life plays an important role with permanent brachytherapy. New dosing time variables include pulsed RT\textsuperscript{16} and ultra-high dose rate RT known as FLASH.\textsuperscript{17} A recent report of pulsed RT delivered 60 Gy in 2 Gy fractions for newly diagnosed glioblastoma, along with temozolomide. This may sound rather boilerplate, however, the 2 Gy fractions were delivered via ten 0.2 Gy pulses at 3-minute intervals.\textsuperscript{16} FLASH is another novel strategy opening new radiobiological perspectives. Reports have often included similar nominal doses to standard RT but with FLASH, treatment is given within fractions of a second, often shorter than 0.1 second, as opposed to the more typical several minutes. To date, clinical data regarding pulsed RT are more extensive than with FLASH, but both propose decreased normal tissue toxicities with equal to improved tumor control.\textsuperscript{16,17}

Outcomes with \( ^{131}Cs \) GammaTile brachytherapy may be more favorable based upon dose rate, but also upon treatment timing, precise implant topography, source geometry, and beam energy with rapid dose tapering to reduce risks of adverse normal tissue effects, radiation necrosis, and wound distress.\textsuperscript{18} Within this issue you will find reports and reviews of available data with CNS brachytherapy—when applicable with GammaTile—for glioblastoma, meningioma, brain metastasis, and spinal tumors, among others, as well as suggestions for new opportunities.

RT is largely therapeutic light. The light sources are expanding, and with them opportunities to enhance patient care, to improve tumor control and to minimize adverse events. But as with most human uses for light, how one points it is vital. Brachytherapy remains noteworthy for the precision with which it hits the focal point.

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**References**

1. Glasser O, Röntgen WC. Dr. W.C. Röntgen. 2nd ed. Springfield, IL: Charles C. Thomas; 1958.
2. Pasachoff N. Marie Curie and the science of radioactivity. New York, NY: Oxford University Press; 1996.
3. Bolot J. Radiotherapy in Skin Disease. London: Rebman Limited; 1905.
4. Grubbe EH. X-rays in the treatment of cancer and other malignant diseases. Med Rec. 1902;62(18):692–695.
5. Goldberg SW, London ES. Zur frage der Beziehungen zwischen Becquerel-strahlen und hautaffectionen [On the question of relations between Becquerel rays and affections of the skin]. Dematol Zeitschr. 1903;10(5):457–462.
6. Knox R. Radiography and Radio-therapeutics: Radio-therapeutics. London: Macmillan; 1918.
7. Patel RR, He K, Barsoumian HB, et al. High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: results of a phase II trial. Radiother Oncol. 2021;162:60–67.
8. Hirsch O. Uber Radiumbehandlung der hypophysentumoren. Arch Laryng. 1919;34:133, footnote 20.
9. Hirsch O. Symptoms and treatment of pituitary tumors. Arch Otolaryngol Head Neck Surg. 1952;55(2):268–306.

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10. Frazier CH. The effects of radium emanations upon brain tumors. Surg Gynecol Obstet. 1920;31:236–239.
11. Choi M, Zabramski JM. Re-irradiation using brachytherapy for recurrent intracranial tumors: a systematic review and meta-analysis of the literature. Cureus. 2020;12(8):e9666.
12. Bartek Jr J, Alattar AA, Dhawan S, et al. Receipt of brachytherapy is an independent predictor of survival in glioblastoma in the Surveillance, Epidemiology, and End Results database. J Neurooncol. 2019;145(1):75–83.
13. Laperriere NJ, Leung PMK, McKenzie S, et al. Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. Int J Radiat Oncol Biol Phys. 1998;41(5):1105–1011.
14. Selker RG, Shapiro WR, Burger P, et al. The Brain Tumor Cooperative Group NIH trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. Neurosurgery. 2002;51(2):343–355; discussion 355.
15. Brachman D, Nakaji P, Smith K, et al. Resection and surgically targeted radia-
tion therapy for locally recurrent GBM. J Clin Oncol. 2021;39(suppl. 15):2054.
16. Almahariq MF, Quinn TJ, Arden JD, et al. Pulsed radiation therapy for the treatment of newly diagnosed glioblastoma. Neuro Oncol. 2021;23(3):447–456.
17. Wilson JD, Hammond EM, Higgins GS, Petersson K. Ultra-high dose rate (FLASH) radiotherapy: silver bullet or fool’s gold? Front Oncol. 2020;9:1–12.
18. Gessler DJ, Ferreira C, Dusenbery K, Chen CC. GammaTile: sur-
gically targeted radiation therapy for glioblastoma. Future Oncol. 2020;16(30):2445–2455.