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Late Effects from Hadron Therapy

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Abstract

Successful cancer patient survival and local tumor control from hadron radiotherapy warrant a discussion of potential secondary late effects from the radiation. The study of late-appearing clinical effects from particle beams of protons, carbon, or heavier ions is a relatively new field with few data. However, new clinical information is available from pioneer hadron radiotherapy programs in the USA, Japan, Germany and Switzerland. This paper will review available data on late tissue effects from particle radiation exposures, and discuss its importance to the future of hadron therapy.

Potential late radiation effects are associated with irradiated normal tissue volumes at risk that in many cases can be reduced with hadron therapy. However, normal tissues present within hadron treatment volumes can demonstrate enhanced responses compared to conventional modes of therapy. Late endpoints of concern include induction of secondary cancers, cataract, fibrosis, neurodegeneration, vascular damage, and immunological, endocrine and hereditary effects. Low-dose tissue effects at tumor margins need further study, and there is need for more acute molecular studies underlying late effects of hadron therapy.

Introduction

Hadron therapy is the use of charged particle beams of protons or carbon ions for radiotherapeutic treatment of disease or abnormal conditions. Hadron therapy holds promise due to its ability to deliver high doses of radiation to sharply defined target volumes. Heavier particles have a somewhat diminished depth-dose profile, but enhanced biological effectiveness. This is a rapidly growing field as witnessed by the growing number of patients treated with proton (up to 33,398) or heavy ion (up 3,860) beams, and the growing number of new facilities currently under construction throughout the world [103]. This is particularly true for proton accelerators, but is significantly more limited for facilities capable of accelerating heavier ions such as carbon. There are currently twenty-four proton facilities worldwide, and nearly twenty more planned, while there are just three carbon facilities currently treating patients, one in Germany and two in Japan, but five future heavy-ion facilities are planned in both Europe and Asia.

There have been some editorial discussions on both sides of the cost-benefit-analysis of hadron therapy (compared to X-ray radiation therapy), and how successful its move from the laboratory to the clinic has been [45, 46, 50, 97]. At issue is the fact that operating technology for accelerators in the laboratory can be underestimated in the transition to the clinic. However, recent reports of overall higher local control and cure rates following hadron therapy [24, 30, 32, 38, 70, 72, 80, 81, 83, 98, 101, 107] have drawn attention to these modalities, and justify a consideration of potential late radiation effects in surviving patients. The goal of this paper is to summarize the few clinical and experimental data that are available, and to suggest areas of need for further study.

Radiation sensitivity among adult human organs

Ionizing radiation injures normal cells and tissues through various molecular pathways. In general, the radiation sensitivity of a given tissue, and in turn of a given organ, depends on the radiation sensitivity of the key cells in the system. Radiosensitive organs with approximate tolerance doses of less than 2 Gy (beyond which there is a high probability of delayed injury within 5 years) include the testis, lens, and ovary. Organs with mid-range sensitivity (<30 Gy) by this index include kidney, lung, bone marrow and liver. More radioresistant organs (<60 Gy) are spinal cord, intestine, urinary bladder, and bone [37]. The brain has historically been considered a radioresistant organ, but recent novel assessments of stem cells in the brain have triggered a reevaluation of the radiosensitivity of specific brain compartments [110].

Also important in radiation sensitivity are several physical and biological variable: dose size, dose mode (internal or external), dose-rate, fractionation, size of the irradiated field, time of observation after exposure, and condition of the stroma and vascular supply. The implementation of hadron therapy has stimulated estimates of not only the absorbed physical dose, but also a biologically weighted dose that includes a medical decision and clinical judgement [115]. The ICRU has made recommendations for international standardization of these units for protons [51]. The ICRU has another report in preparation regarding prescribing, recording and reporting proton beam therapy.

Acute versus late effects

Radiation lesions demonstrate differences in their temporal appearance. Immediate injury of radiosensitive cells is usually associated with DNA damage in the rapidly proliferating cells. Progressive necrosis and loss of epithelial cells occurs with denudation of villi, hemopoietic, spermatogonia and spermatocyte depletion in the early phase within days of an exposure.

Recovery processes begin with repair and repopulation of stem cell pools within individual tissue compartments and continue for months. Delayed effects begin months to years after the exposure with atrophy, necrosis, metaplasia, atypia, dysplasia and neoplasia in epithelial compartments, fibrosis, fibrinous exudate, atypical fibroblasts, and lack of cellular inflammatory response in stromal compartments, and finally alterations in capillaries and arterioles in the vascular compartment. For successful radiotherapy, the most important aspect is often finding the balance between cure and late effects (see [33])

Radiations with enhanced ionization densities can cause both quantitative and qualitative differences in cells and tissues compared to radiations with sparse ionization [8, 15, 17, 118, 120]. At issue for this paper are differences in late tissue effects induced by gamma rays, protons, helium, carbon or heavier ions. Due to its earlier clinical establishment, proton therapy has a longer follow-up experience than carbon ion therapy. Biological studies with experimental systems are still ongoing for both radiation types.

Proton and helium radiation therapy

The superior radiation depth-dose profiles due to the physical characteristics of proton and helium beams can be used to treat small volumes of tissue very precisely, while sparing surrounding normal tissues. Many of the initial radiotherapeutic uses of protons have been to treat lesions in the head and neck region. An elegant demonstration of the precision of the proton beam is the work of Reder et al [91] who studied the physiology and morphology of the cat lateral geniculate nucleus (LGN) following proton irradiation. The LGN is a structure with well-defined anatomical boundaries, and well-described afferent, efferent, and receptive field properties. Reder et al. [91] used a 1.0 mm proton microbeam to determine short-term (3 month), and long-term (9 month) receptive field effects of irradiation on LGN relay cells after 16, 40, or 60 Gy. Following irradiation, abnormalities in receptive field organization were found in 40 and 60 Gy short-term animals, and in all of the long-term animals. The abnormalities included "silent" areas of the LGN receptive fields. Histologic analysis failed to identify cellular necrosis or vascular damage in the irradiated LGN, but revealed a disruption in retinal afferents to areas of the LGN. Unexpectedly, the area and extent of neural function increased with time, having larger effects with longer post-irradiation time suggesting that cellular mechanisms initiated by protons continued for extended time after exposure.

The treatment of human lesions with protons or helium ions was pioneered in Berkeley, Uppsala, Sweden, Harvard and in the former Soviet Union (see review in [89, 90]). There is an impressive literature in particular with regard to treatment of chordoma/chondrosarcoma [12, 21, 22, 32, 80, 84, 92, 95, 105, 107], meningiomas [59, 114] and choroidal melanoma [24, 28, 29, 34, 48, 89, 92]. Combinations of photons with a proton boost have been shown to offer an exceptional chance of cure at the price of an acceptable toxicity [83]. Few detailed reports of late morbidities following proton therapy [113] have been reported. Experimental studies looking at dose-volume effects in the rat cervical spinal cord after proton irradiation showed steeply increasing ED₅₀ values for lengths of less than 8 mm [14]. The results suggested the presence of a critical migration distance of 2-3 mm for cells involved in regeneration processes.

Tumors in numerous additional organs of the body have been treated with protons or helium ions for evaluation of tolerance and therapeutic efficacy, including liver [7, 73, 74], stomach [62, 100], esophagus [63], lung [101], prostate [102, 104], pancreas and biliary duct [122] and gynecologic sites [6].

A more significant issue for evaluation of proton therapy is: which photon modality should be the gold standard therapy for comparisons with protons? Conformal proton radiotherapy (PRT) has been compared to three-dimensional (3-D) planned photons in evaluation of limiting dose to auditory structures [69] and brain lesions [9]. The conclusions drawn indicate that for simple geometries or for superficial lesions, there is no advantage in using protons. However, for complex planning target volumes (PTV), or when the PTV is in the vicinity of critical structures, protons seem to be potentially better than for the fixed-field photon technique. In the case of posterior fossa conformity, 3D photons came at the expense of increasing amounts of normal tissue receiving low to moderate doses, whereas PRT resulted in increased dose sparing of normal structures. However tumor recurrence was neither prevented nor noticeably delayed in dose-escalation Phase I/II trials with proton/photon irradiation compared to published series on photon irradiation for Daumas-Duport lower-grade [38].

Intensity modulated radiotherapy (IMRT) is one of the newest photon developments allowing nearly ideal delivery of photon beams. The promise of this innovation is much greater local control rates with reduced morbidity [26] and see summary of recent International 3D-CRT/IMRTWorkshop [52]. However, Hall and Wu, [49] point out that the move from 3D-conformal radiotherapy to IMRT involves more fields, and the dose-volume histograms show that as a consequence, a larger volume of normal tissue is exposed to lower doses, and there is increased total body exposure from leakage radiation. Both of these factors would increase the risk of second cancers. This risk is especially an issue for pediatric neuro-oncology [71]. With regard to proton therapy for pediatric cranial tumors, early treatment-related morbidity associated with proton therapy is low and decreased long-term toxicity in the maturing child is expected [43, 75]. A comparative analysis of the incidence of secondary cancer after therapy for Hodgkin's disease with photon or proton radiation indicated that IMRT has little or no improvement over conventional treatments. However, proton treatments could result in a significantly lower cancer incidence than photon treatments, and this result appeared to be independent of the delivery technique [94]. Anecdotal increased head and neck tumors have been reported for proton-irradiated rodents and non-human primates [31, 121].

Additional late effects of protons or helium include cataract-induction [16, 35, 47, 68, 77, 82] late retinal cell damage [117], endothelial cell loss in retinal microvessels [5] and optic nerve (125), loss of endocrine function [104] and immunological deficits [54-56, 88]. The majority of these studies conclude that late effects induced by protons or helium ions are nearly equivalent to what one would expect from equivalent photon doses. Proton RBE values are 1.0, except near the very end of the stopping Bragg peak [10, 11, 13, 44, 53, 86, 87]

In conclusion, there is strong evidence supporting the use of proton radiotherapy as superior even to IMRT [40] and perhaps even as a replacement for external beam radiation therapy [106].

Carbon ion beam radiation therapy

One would expect that late radiation effects from densely ionizing radiations like carbon or neon ions may be a greater risk than late effects from less densely ionizing radiations. The neutron experience taught us that late effects of high-LET radiations can have a higher RBE than the acute effects from neutrons [119]. A handicap in the evaluation of late effects is that the follow-up time of patients treated with carbon or neon ions is considerably shorter than patients treated with protons [23, 25, 57, 70, 78, 79, 98, 99, 111, 112].

The choice of tumors to be treated with carbon ion beams, and the modes of delivery have been different for the three facilities currently treating patients. At the HIMAC facility in Chiba, Japan, and the HYOGO ion beam medical center in Hyogo, Japan, carbon beam radiotherapy uses wobblers magnets and a scatterer to flatten the radiation field. The depth-dose distribution of the beam is modified with passive beam filters to spread-out the Bragg peak [58]. The Japanese program has concentrated primarily on tumors of the chest and abdomen (lung, liver, uterine cervix, and prostate), and also treated head and neck patients. Overall carbon treatment schedules have been successfully shortened to one to three weeks for liver and lung cancer, which minimized the proliferation of tumor cells during treatments [58]. The Japanese program was a pioneer in the development of particle beam delivery gated to respiration. The Japanese program also uses RBE determinations from the laboratory, and modified by clinical judgement to implement their beam delivery [42, 53, 108].

In contrast, the German carbon ion program ongoing in Darmstadt, Germany uses active beam shaping by scanning in 3D [18, 64, 65]. The German program has restricted their carbon radiotherapy to tumors of the head and neck. This conservative approach was important to their assessment of the active beam delivery in organs without body motion. The German program uses a theoretical model of local effect to estimate biological effect of the carbon ions based on laboratory measurements and clinical judgements [66, 67, 96, 116]

For all of the reasons mentioned above, much of what is known about late effects of heavier ion beams has largely been obtained in the laboratory, and clinical impressions from the earlier neon clinical trials in Berkeley [25]. Late effects on the brain [60, 61] and spinal cord [85] have been emphasized, and the data show evidence indicating that the RBE values for single-dose irradiations of the brain and spinal cord are within the experimental uncertainty. It was noted that vascular dilatation, erythrocytic stagnation and hyperpermeability are evident in the delayed injury to the spinal cord [85]. Changes in bone volume after irradiation have also been noted and linked to differential modulation of radiation-induced growth factor expression [93].

Significant differences in RBE values are obtained with carbon ions depending on the radiation quality and the biological model studied [41, 108] and accelerated reoxygenation has been reported after fractionated carbon ions, compared to γ -rays [2]. Significant and rapid tissue remodeling has been reported for heavy-ion damage compared to low-LET radiation *in vivo* [36] and in cells *in vitro* [39]. The induction of gene and protein expression patterns are also LET-dependent [3, 4, 20, 27, 76, 109]. Finally tumor induction is increased by high-LET radiations [1, 19].

In conclusion, the significance of the increased biological effectiveness of heavy ions is a two-edged sword. There is clinical evidence for efficacy in the treatment of non-squamous cell histology such as adenocarcinoma, adenoid cystic carcinoma, and malignant melanoma, early stage and locally advanced non-small cell lung cancer, hepatoma, and bone/soft tissue sarcoma. Radioresistant, slow-growing tumors also respond. However, if the carbon treatment volume includes normal tissues, they too are at risk for the appearance of both enhanced acute and late radiation effects. The skill of the physicist is required to assure optimal treatment plans for reduction of extraneous dose to normal tissues surrounding the tumor target, but carbon ions hold the potential for significant clinical advantage not achievable with protons.

Summary

New radiation modalities require many years for full evaluation of late-appearing effects. Proton therapy has survived this gauntlet, and evidence for its efficacy in the clinic now indicates it may well be superior even to the best photons has to offer (IMRT) for deep and complicated tumor sites. Late tissue normal tissue toxicities do not appear to be an issue for proton therapy. Carbon ion therapy currently has a shorter follow-up, and in fact it is premature to draw clinical conclusions regarding long-term normal tissue toxicities. However, early clinical evidence is mounting that indicates there is a place for ion-beam therapy where tumor radiation resistance to proton therapy is an issue. Careful carbon treatment planning has led to acceptable acute normal tissue reactions, and late reactions are currently under scrutiny. One deficiency for both proton and carbon ion therapies has been the lack of information on the course of metastatic disease. Overall, it may be that the radiation oncologist would select protons for specific discreet deep lesions in some tissues, and carbon ions for specific discreet lesions in other tissues of the body, but that neither modality alone may be adequate for diffuse, highly metastatic lesions.

Acknowledgements

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