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Review

From clinical observations of intensity-modulated radiotherapy to dedicated *in vitro* designs

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ABSTRACT

In this review, an overview of intensity-modulated radiotherapy (IMRT) and related high precision radiation techniques is presented. In addition, the related radiobiological issues are discussed. Hereby, we try to point to the potential differences in radiobiological effect between popular intensity-modulated radiotherapy and related techniques (IMRT+) and conventional or three-dimensional radiotherapy (3D-RT). Further, an overview of the existing *in vitro* and *in vivo* radiobiological models to investigate the effect of spatially and/or temporally fractionated dose distributions, as applied in IMRT+, on the biological outcome is given. More in detail, our radiobiological models will be presented. Additionally, we will discuss the (dis)advantages of the presented models, and give some consideration to improve the existing radiobiological models in terms of set-up and clinical relevance.

Contents

Abbreviations: 3D-CRT, conventional or three-dimensional radiotherapy; 3D-RT, three-dimensional radiotherapy; C-IMRT, compensator IMRT; cRT, conventional radiotherapy; CV, crystal violet; DMSO, dimethylsulfoxide; IMAT, intensity-modulated arc therapy; IMRT, intensity-modulated radiotherapy; IMRT+, intensity-modulated radiotherapy and related techniques; MLC, multileaf collimators; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide; MN, micronuclei; OD, optical density; S-Arc, single arc techniques; SLDR, sub-lethal damage repair; STFDD, spatio-temporal fractionated dose distribution; SW-IMRT, sliding window IMRT; SS-IMRT, step-and-shoot IMRT.

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1. Intensity-modulated radiotherapy (IMRT) and related radiobiological issues

The technology to deliver radiation therapy has been enormously changed during the last decade. IMRT and related high precision radiation techniques created the possibility to generate dose distributions that can be tailored to fit tumors of a complex geometrical shape while avoiding nearby or even surrounded radiosensitive normal tissues. The delivery of these techniques disregards the basic paradigm of earlier technology called conventional or three-dimensional radiotherapy (3D-CRT) which

used beams that covered the entire target with an intensity that was either uniform or linearly increasing in one direction across the beam's cross-section. Using these earlier techniques, beams were delivered in quick succession with each beam contributing significant dose to the entire target and the total delivery procedure taking less than 4–10 min.

An unifying principle of IMRT and related techniques, further called IMRT+, is the sequential use of numerous small beams which irradiate each only part of the target but temporally combine to generate radiation dose clouds that cover the entire target. Consequently, the target tissue is exposed to a spatio-temporal fractionated dose distribution (STFDD). IMRT+ differs substantially in the way they deliver the spatial as well as the temporal component of the STFDD. The spatial component ranges from a few tenths of dose depositions to parts of the target (e.g. IMRT close-in step-and-shoot techniques) to many thousands (e.g. serial or helical tomotherapy techniques) to deliver a single radiation fraction. Likewise, to deliver the fraction dose to each part of the target, the temporal component ranges from a sequence very short interruptions of dose deposition over a few minutes (e.g. mono-arc techniques like VMAT or RapidArc) to thousands of interruptions—with some of substantial length—over more than an hour (e.g. CyberKnife when used for large targets). The determination of the radiobiologically relevant features of the resulting 4D dose distribution – time being the 4th dimension – is extremely challenging but necessary. This task is different from the early attempt to quantitatively characterize the spatial beam modulation from a delivery point of view as undertaken by Webb in 2003 [1]. Indeed, the degree of absorbed dose modulation – rather than the degree of applied beam modulation – should be taken as the basis for making radiobiological inferences.

At least 2 contemporary evolutions further complicate the radiobiological interpretation of various IMRT+ approaches: techniques to irradiate moving targets (gating, freezing, and tracking) and the increasing popularity of hypo-fractionation.

STFDDs differ enormously between the various IMRT+. For a homogeneous 2 Gy fraction, the biological effect of some IMRT+ may closely resemble that of the 3D-CRT. For other techniques substantial differences can be expected. Assuming that *in vitro* observations listed in Table 1 are relevant in the clinic, we hereby try to point to the potential differences in radiobiological effect between popular IMRT+ and 3D-CRT.

1.1. Static beam IMRT techniques

IMRT can be delivered in a very robust way by the use of physical compensators that are put in the beam line [2]. IMRT using compensators will require entering the treatment room to change compensators between beams. Entering the room in-between three-dimensional radiotherapy (3D-RT) beams will also be needed in case of non-coplanar set-up or manually inserted wedges. Overall, multi-beam compensator IMRT (C-IMRT) is roughly comparable to 3D-RT regarding the time needed for delivering a 2 Gy fraction; typically less than 10 min. Little or no evidence exists that cell survival is significantly affected by variations of temporal fractionation schemes within a maximum of 10 min overall delivery time. C-IMRT allows creating extremely steep dose gradients. In such cases spatial fractionation by single beams will be very different between compensator IMRT and 3D-CRT but gradients will average out by integrating multiple beams. Whether bystander effects across temporally spaced opposed gradients will average out is unknown. Overall, C-IMRT can be expected to provide mostly similar cell survival as 3D-CRT after delivery of a homogeneous 2 Gy fraction.

The use of physical compensators went rapidly out of fashion with the advent of computer controlled multileaf collimators (MLC) in the mid-90s. One MLC technique mostly uses a narrow window consisting of all of the leaves that cover the length of the target and sweeps this opening across its volume. The exact size of the opening for each leaf pair is modulated according to the desired dose at each point in the target volume [3]. This sliding window method is often implemented in a continuous dynamic fashion to speed up the dose delivery. Earlier implementations required reduced dose rates of the linear accelerator. Together with the relative inefficiency of sliding window as compared to compensator IMRT, overall delivery times increased by a factor of 2–3 times. Biologically, 2-Gy delivery times exceeding 15–20 min raise questions of temporal fractionation. This would translate to local average dose rates lower than 14 cGy/min for which increased cell survival can be expected. Another popular IMRT approach used superimposed static fields from each beam direction that are sequentially delivered. The beam is halted during the transition from one field to the next when the MLC leaves accomplish the required motion [4]. The delivery is performed as step-and-shoot sequences with beam-off during the leaf motion (step) and beam-on (shoot) with fixed collimator aperture. Regarding spatial and temporal fractionation, the same reasoning as for sliding window can be made although the final dose distribution of step-and-shoot IMRT (SS-IMRT) tends to be less smooth. Over the last decade, delivery efficiency has increased. Modern implementations of sliding window IMRT (SW-IMRT) and SS-IMRT are efficient and probably biologically comparable to C-IMRT regarding their temporal component.

1.2. Single-arc techniques and IMAT

Intensity-modulated arc therapy (IMAT) by means of standard MLC was invented by Yu in the early 90s [5]. Recently, IMAT-related single-arc techniques were developed, their common property being the delivery of a 2-Gy fraction within one or a few minutes, much faster than static beam IMRT techniques and even faster than multi-beam 3D-CRT. Although spatial and temporal modulation occurs at high mean frequency the biological effect of mono-arc techniques may closely resemble that occurring after

Table 1
Current radiation therapy modalities with number of corresponding radiobiological papers found in Web of Science.

	Search keywords phrase in Web of Science	No. of papers
CyberKnife	Topic = (CyberKnife and radiobiology)	3
Tomotherapy	Topic = (tomotherapy) AND Topic = (radiobiology)	3
IMAT	Topic = (IMAT or VMAT or RapidArc) AND Topic = (radiobiology)	1
S-Arc	Topic = (arc AND radiobiology) + *manual inspection*	0
SW-IMRT	Topic = (IMRT and radiobiology and sliding window)	1
SS-IMRT	Topic = (IMRT and radiobiology) + *manual inspection*	1
C-IMRT	Topic = (IMRT and radiobiology) + *manual inspection*	0
3D-RT	Topic = (conformal and radiotherapy and radiobiology) NOT Topic = (IMRT)	25
cRT	Topic = (radiotherapy and radiobiology) NOT Topic = (IMRT) NOT Topic = (conformal)	768