

Novel Radiotherapy Schedules Aid Recovery of Normal Tissues after Treatment

Jack F. Fowler

Emeritus Professor of Human Oncology and Medical Physics

Medical School of the University of Wisconsin at Madison, USA

In this issue, a paper by Tomuleasa et al [1] deals with the self-renewing properties of human liver tumor cells and their capacity to form stem cells, even when cultured with some chemotherapy drugs. In the ongoing search for better ways of eliminating malignant cells without doing too much damage to normal tissues it is important to know quantitatively how resistant to chemotherapy or to radiation various types of malignant cells might be, compared to normal tissue cells.

Head and neck cancer is now one of the types of cancer that can be treated with radiotherapy, chemotherapy and/or surgery to give 5-year survival of patients of 60 to 80% even with stage IV advanced disease [2]. Although the tumors are mostly epithelial, the tissues that are also treated in any method of dealing with cancers involve many mesenchymal normal tissues. We need to find out all we can about the pathways of damage and repair caused by treatment agents including drugs and radiation. The properties of hepatic cancer stem cells, with their well known abilities to proliferate to replace excised liver mass, make them good candidates for these types of investigation.

Treatments of head and neck cancer, to stay with the same example, have made great progress in the last two decades, with the use of novel non-standard fractionation schedules and concomitant chemotherapy and also due to advances in surgery. Details of how fractionation works in practice, and how improved fractionation might reduce the need for some of the chemotherapy or surgery, are active areas of research. Differences between the proliferative response during radiotherapy between the tumor and the normal tissues are at the root of the new non-standard schedules.

In another paper, Kaanders et al [3] asks the question: Is acute radiation damage the critical limitation for non-standard

fractionation? This question arises because there are two types of non-standard fractionation possible: hyperfractionation or hypofractionation. Standard fractionation has usually consisted of 32 to 35 “daily” (5 times a week) treatments of 1.8 or 2 Grays, given over 6 or 7 weeks. “Hyper” is many more and smaller dose fractions. “Hypo” is fewer and larger fractions and should be used especially for tumors with unusually low ratios of alpha/beta (the coefficients of irreparable versus repairable radiation damage), of which prostate cancer is the well known example; but occasionally also for very rapidly growing tumors such as rectal or lung cancer, when shorter overall treatments are necessary to avoid tumor cell proliferation.

For avoiding late complications (more than 6 months after radiotherapy) we have known since 1980 how to restrict total doses and volumes irradiated to keep a low probability of the late complications, using Linear Quadratic cell modeling with the famous (or notorious, if you don't like mathematics) alpha/beta radiosensitivity formula. Because the relevant slowly repopulating “late” tissues have low ratios of that alpha/beta ratio, more and smaller dose fractions (the “hyper” option) are always better at sparing late complications; so “hyper” ruled for several generations and schedules became longer and longer. Until they became too long, at 7 or 8 weeks, so that tumor cell proliferation became a hazard that could then prevent effective cures [4].

“Hypo” instead (shorter schedules) was tried, but the acute reactions were sometimes too severe, hence Kaanders' very appropriate question. He was right about the shorter schedules, unless a very precise dose reduction could be made, which did not reduce total dose too much. How much was too much and how could the best compromise be worked out?

No such modeling to help avoid acute reactions was available until 2003 [5], after some ground-breaking human biopsy studies by a radiobiologist from Germany and a clinical team in Australia [6], who found that after starting daily irradiation, repopulation begins in normal mucosa as soon as 7 days - several weeks before it does so in tumors at 21 to 32 days. It is this difference that drives the whole pattern of optimum fractionation, together with the important

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Address for correspondence:

Prof. Jack F. Fowler, DSc, PhD
150 Lambeth Rd
London SE1 7DF
United Kingdom
E-mail: jackfowlersbox@gmail.com

difference of treating twice a day instead of only once a day. This difference is crucial to the optimum overall times to choose for non-standard treatment schedules. The over-long schedules using many small dose fractions can be safely recast as shorter schedules using two fractions a day. The advantages of shorter overall times without the disadvantage of large dose-per-fraction can then be used [7]. Some of the best compromises for head and neck treatments have been published as recently as 2008. Good optimum dome-shaped curves, with a smooth set of maximum values at carefully modeled overall times, can now be predicted. It turns out that two fractions a day of 60×1.3 Grays, but in 43 days instead of the obviously convenient 39 days, are ideal. It is only if we have tumors of unusually fast doubling times, less than 3 days, that we would want to use schedules as short as 3 weeks with one fraction a day of nearly 3 Gy.

Such optimized schedules can improve on the previous empirical schedules by approximately 4 to 8 Gy, equivalent to 7% to 13% increase in tumor dose, with no increase in normal tissue dose; and estimated as 10 to 20% increase in loco-regional control.

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